THE MEDICAL JOURNAL OF AUSTRALIA

VOL. I.—28TH YEAR. SYDNEY, SATURDAY, MARCH 15, 1941. No. 11.

Table of Contents.

ORIGINAL ARTICLES— Page.
The Freedom of the Medical Profession, by Arthur E. Brown .. 315
The Iso-Agglutinin Titre of Pooled Serum or Plasma, by Rachel Jakobowicz and Lucy M. Bryce .. 318
Experimental Measles: Transmission of the Disease to Monkeys, Failure to Transmit Measles to Rabbits, Cultivation of the Virus on the Chorio-Allantoic Membrane, by E. Weston Hurst and Barbara Cooke .. 323

REVIEWS—
Periodicity in Cancer .. 329
A Text-Book of Bacteriology .. 330
Biological Aspects of Infectious Disease .. 330
A Handbook on Radiography .. 330

LEADING ARTICLES—
The Mental Hospitals of New South Wales .. 331

CURRENT COMMENT—
Plasma Prothrombin and Vitamin K .. 332
Pulmonary Hypertension .. 333
"Highways to Health" .. 333

ABSTRACTS FROM MEDICAL LITERATURE— Page.
Surgery .. 334

BRITISH MEDICAL ASSOCIATION NEWS—
Scientific .. 336

NAVAL, MILITARY AND AIR FORCE—
Appointments .. 343

OBITUARY—
Eric Bailhache .. 343
Keith Russell Moore .. 343
George Gordon Owen Phillips .. 344

CORRESPONDENCE—
A Method of Covering Skin Grafts .. 344

NOMINATIONS AND ELECTIONS .. 344

CORRIGENDUM .. 344

DIARY FOR THE MONTH .. 344

MEDICAL APPOINTMENTS: IMPORTANT NOTICE .. 344

EDITORIAL NOTICES .. 344

THE FREEDOM OF THE MEDICAL PROFESSION.

By ARTHUR E. BROWN,
Colac, Victoria.

FREEDOM or its absence can only be relevant when one considers how it affects the execution of a man's wish and desire to make a good job of what he sets his hand to.—A.G.B.

A cardinal characteristic of the principle of evolution in the world of living things is the increase in complexity. The one-celled amœba which lives its humble life in its own self-contained manner is far removed from many-celled man, with his multitudinous specialized cells, each called upon to perform a special function towards the maintenance of the well-being of the conglomerate mass which makes up the individual *Homo*. The path leading from the one simple to the other highly complex organism leads along two main lines, without which no such evolution would be possible: the lines of specialization and coordination.

The analogy between biological evolution and social evolution is so exact as to be almost identical. On the evolutionary road from the single family group to the complex modern State there are precisely the same stages of development along the same lines of specialization, central coordination and interdependence. No man in the modern state is free in the sense in which a lone man is free. The existence of every individual is conditioned by the proper functioning of all other individuals in the community, exactly as is that of the individual cells in the human body. Every specialized group of people is dependent for its well-being on the proper functioning of all the other groups. The powerful alert muscles of the swallow's wing depend for their proper functioning on the proper working of the nerve cells of the swallow's brain, of the digestive cells in its alimentary tract, and of the excretory cells of its eliminating apparatus. And equally the specialized social groups of miners, or doctors, are dependent for their prosperity, their well-being, and even for the proper performance of their social functions, on the normal active cooperation of all the other specialized groups in the community. And to that extent each member and each group is by so much the less "free". Selfish, antisocial or inefficient working on the part of any one group brings in its train a communal malaise which reflects immediately on all other groups. The more complex, or as we call it, the more civilized, a community grows, the more this interdependence replaces the older independence. And we accept all this gladly, and rightly or wrongly call it progress. The man who lights his hut by tallow candles made from the fat of sheep reared and killed by himself on his own land is free in respect of his light. The man who switches on light brought by wires from a powerhouse some hundreds of miles from his home is by so much the less free. But he makes no complaint of his lack of freedom. He is on the other hand a little complacent about the better quality and convenience of his lighting. Which epitomises in little our general attitude towards the complexity and increasing interdependence of our social life. None the less, every major piece of social reorganization involving further specialization involves also a further degree of centralized control and a further loss of individual freedom of action. We may regret the passing of the individual freedom. We may be right in regretting it. But whether we do or not, we have the fact to face that our social system, with its growing complexity of structure, needs and demands a correspondingly increasing degree of organization, and therefore asks for further restrictions on the absolute freedom of the individuals and groups. We must accept this complex

material scheme of life as the one in which our fate has placed us; and those men who are anxious to benefit their fellows will endeavour to fit as snugly as possible into the closely dovetailed mosaic of trades, businesses and professions which compose it, to make them approximate more nearly to the needs of changing society. They will not be deterred from doing so by an abstract thought of some diminution in their personal liberty, recognizing that in the smoother working of the social machine there will be found compensating benefits for them as for all men.

These thoughts have been born in me owing to various comments which have been made on my recent suggestion for a reorganization of the medical profession to a form better fitted to the social framework in which we now work. There has been very little discussion of the primary question as to whether such a scheme would in fact be an advantage to medical science and a benefit to the community at large; but almost all criticism has been with variations on the theme of "totalitarianism", "communism", or "This is exactly what we are now fighting against", that such a scheme would mean the abandonment of the freedom of the medical man. And I want to protest entirely against that attitude of mind.

And here may I draw your attention to the quotation which I have put at the head of this paper to serve as the text of my sermon: "Freedom or its absence can only be relevant when one considers how it affects the execution of a man's wish and desire to make a good job of what he sets his hand to", and to consider, in the light of that aphorism, just what sort of freedom of ours it is that is endangered. Absolute abstract freedom, of course, we do not possess, and never have possessed, either as individual members of the community or as craftsmen in our profession. What freedom we do possess now, that we should not possess in a National Medical Service? And what disadvantage to ourselves and to the public would result from the loss of such freedom?

At present we are free to act and practise as we think best, with only such relation to the public need as is contained in the economic law in relation to supply and demand. We have the freedom to choose our place of work and residence irrespective of whether our services are required there or not, making our decision only on the grounds of what money we can make there. We have the freedom to let our brains stagnate and be idle if we wish; to do good work or bad without supervision; and to vie with quack medicine vendors in empirical treatment for profit. It is to our credit as a profession that more of us do not take fuller advantage of that freedom. We are free to treat two-thirds of our patients for nothing, and to make our living by charging the other third, who can pay us, more than they should rightly pay for our services. We are free to waste money and energy and our natural spirit of good fellowship in needless competition with our colleagues. We have the freedom to choose the interesting and profitable lines of work, and to leave the all-important subject of preventive medicine to those few who are sufficiently interested in it to undertake it.

There is nothing inherently valuable to ourselves, and certainly nothing valuable to the community in our freedom to do all these things. There is only one form of freedom which we should value and fight for to the utmost of our strength, and that is the freedom to act according to the best of our knowledge and skill in the interests of our patients. Theoretically we have that freedom now. Those who have been so successful in their work that they have attained to some degree of mental and financial independence, undoubtedly have it. To those of us who are harassed by financial difficulty or by overwork, its possession is very theoretical indeed. This is the type of freedom which is now, in my view, threatened. Not threatened by the profession's organizing itself into a coordinated whole for the benefit of the community; but threatened, if we stay as we are, by the increasing financial stresses of which young practitioners are very conscious; and even more threatened if we remain passive, by our being organized from outside by politicians and by the enforced application to our work of bureaucratic and rule-of-thumb methods applied to work for which they are most eminently unsuitable. I believe most firmly that social forces are already at work which, if we make no move ourselves, will in the comparatively near future swamp us entirely and take away from us that freedom to which we should hold most firmly, while also incidentally sweeping away our freedom to do those other things which most of us would in our hearts be quite well content to see vanish.

Everywhere on the economic side of life we have seen in the past century or so the small independent craftsman, tradesman or manufacturer steadily and inexorably absorbed into larger and larger amalgamations of business or manufacture, and the process is still going on with undiminished momentum. There is something to regret in the passing of the independent craftsman; but it has been an inevitable accompaniment of the development of the machine civilization to which we are, whether we like it or not, committed. It has been more and more accepted as axiomatic that essential public services must be either directly under central State control, as for instance the railways are in Australia, or under close State supervision, as are, for instance, the distribution of food and milk supplies. New essential services are developed under State control from the start, as has been the broadcasting service in England. Services of a less material nature, such as education, have for long been recognized, owing to their importance to the State, as being mainly a proper function of the central government. No one, I think, would be eager to claim that a satisfactory job has been made of that, at any rate here in Australia; but would anyone conceive it possible nowadays to leave the education of our children to the mercy of such individual schoolmasters as felt they could make a living by opening a school in this or that country town or village? The poorness of the education service, as it has been developed under government control, is not a warning to us against our organizing ourselves, even if it is a solemn warning against our letting the new medical service develop under similar conditions. It is certainly no argument in favour of giving up the teaching of our children again into the hands of private sellers of knowledge. It is remarkable indeed that in the midst of this development our own line of service has, almost alone among those of an equal importahce, been allowed to carry the organization of the nineteenth century well on into the twentieth; and even this has been made possible only by the development of more and more parallel or auxiliary services which are under State control, and which now lap round our base in a rising tide that constantly threatens to submerge us.

This point appears to me to be so much more important than merely attaching to any scheme of reform any "thought label", political or otherwise, that I confess I wonder that this process has shown itself so prominently in medical circles as it has. The essence of democracy is the freedom to choose and to alter the form or the personnel of the government, and freely to criticize any and every fault in the administration of the State or its management of its essential services. I cannot see that the organization of any service in the internal structure of a State is evidence of totalitarianism or that it affects the democratic structure of that State. Freedom of thought and freedom of expression are what make a country free and democratic, and I cannot conceive that the organization of a more efficient medical service can even distantly take this freedom away from the men serving in it.

All political systems depend for their success much more upon the spirit in which they are conceived and guided than upon the technical constitution upon which they are built. Democracy itself, paradoxically enough, appears to find its highest and best expression in countries whose constitution is theoretically aristocratic. It works very well in England and in the countries of Scandinavia, which are all monarchies; less well perhaps in America and Australia; and apparently not at all in the republican countries of continental Europe. The cooperative schemes which have made such a difference to the lives of people in Denmark and Sweden, have had a hard struggle to make any impression on the economic life of England, where they

actually originated. The system of control of alcoholism, so successful among the Swedes, would, I am afraid, be found quite unacceptable here because of the apparent loss of personal liberty it involves; although our own method is far more oppressive and far less successful. No system, however good in itself, will work well without three things. It must have a good basic principle, wise leadership and loyal following. No system, however intrinsically bad, is intolerable if it is wisely controlled from the top and loyally supported by the mass of people affected by it. So when I am told that a proposal to systematize the medical services of the State is totalitarian, communistic or socialistic, I am entirely unimpressed. If it is so, then so are our banks, so are our hospitals, so are our country roads boards, so are our electrical and water supplies, so are our postal and telephone systems, so is our education; and all on the same grounds.

In our professional capacity we are not only private traders, selling our knowledge and skill for what it will fetch, for our own profit. We are also the guardians of the health of the nation, and the one hope and standby of those who are sick. And therefore it behoves our pride, both personal and professional, that we should put the medical needs of the community we serve before any thought of our own status, even as in our private work we put the needs of our patients before our own convenience and comfort. Honest thinking is essential. And if any body of men in any country were ever capable of honest thinking, it should, by reason of our training, be ourselves. Honest thinking over the present position of medical service should, even without any additional urge from outside, make us recognize that the organization by which we now serve the public is far from perfect. And it should then be a matter involving our honour for us to be ourselves the first to recognize the fact and the first to take some steps to try to put it right. When to that is added the undoubted fact that public men outside our ranks also have their eyes fixed on the imperfections of our present methods (while, I like to think, also at the same time recognizing the high calibre of the men now practising medicine), then the necessity for us to take charge of the position is redoubled, if we are to forestall plans of change which will be produced by men having far less understanding of the principles involved than we have.

If we are content to sell our knowledge and skill for our personal profit, as a retail tradesman sells his wares, then in spite of the ethics on which we pride ourselves, we must be content to be regarded by the public as merely tradesmen; and the oft-repeated gibe at our main professional association, that it is nothing more than a tight trades union, takes on the colour of truth. If, on the other hand, we are to accept the definition of a professional status, as the placing of the work done first and the remuneration received for it only second, then we cannot in plain honesty be satisfied with less than the best service we can give; and we will accept as professional freedom that system which will best satisfy our wish and desire to make the best of that to which we have set our hands. A hundred years ago, in the first issue of what is now the greatest professional journal in the English language, *The British Medical Journal*, was printed as a statement of the policy of the journal and of the newly formed medical associations the following:

> The maintenance of the respectability of the profession, as it will readily be perceived, necessarily involves the contemplation of those great measures of medical reform which are now engaging the attention of medical practitioners. In the consideration of these we shall at once take the highest ground—that of public utility. The establishment of a system of competent medical education; the securing to the profession a wholesome form of government; the suppression of empiricism; the providing of proper medical attendance for those who are unable to procure it for themselves; and the placing of these and other portions of medical policy under the superintendance of those who are the best acquainted with the subject—are all and each of them but so many ways of advancing the welfare and guarding the interests of the community in general.

Now, a century later, all of us with our lips would be glad to endorse every word of this statement as the policy of our profession. In that century, however, conditions have greatly changed, both inside the medical world in the lines of medical knowledge and treatment, and outside it in the social world. And the "great measures of medical reform which are engaging the attention of medical practitioners" are very different from any that the practitioners of a hundred years ago could possibly have foreseen. That does not, however, seem to me to be a reason why our attitude in dealing with those measures should be any less high than that of our predecessors of 1840. During the century that has passed since that was written, it has become and is becoming more and more evident that the health and welfare of the community in general is rightfully a matter for State concern; and the obvious corollary from that is that the medical services of every sort within the State are also a matter of State concern. No escape from that is possible. The talk about loss of our freedom is not honest talk. Can any one of us, looking round the vast field of preventive medicine lying untouched because it is less profitable or less interesting than our curative work, claim that we are doing our absolute best for the community we profess to serve? In the field of curative medicine we are doing a much better job; in fact a surprisingly good job; but is it the best we could do? Is the presence of five men in a country town, competing with each other for a livelihood, duplicating equipment, keeping clinical notes as personal property unavailable to the others, with the public health work in the hands of one of the five only, and that one handicapped by lack of knowledge, lack of time, lack of interest, and by the fear of treading on the corns of his colleagues—is this a perfect system for the medical care of the folk in the area concerned?

The marvel to me is the fact that we have done as well as we have done; and the fact that we have is a tribute to the mental and ethical calibre of the men who do the work. The old spirit has been a good one, and though many among us have not been able to keep up to its standards in the face of economic pressure, it has on the whole produced good men. We may well lose something of that old spirit by nationalizing our medical service, I know; and the change-over will without doubt bring its own difficulties and imperfections. But we shall surely be serving the public better. And even what we lose may be reduced to a minimum if we ourselves will it so. If we sit back and allow a politically inspired and politically devised State medical service to be forced on the public, our only interest in its creation being a more or less passive resistance, then we as a profession will assuredly get what we deserve, and the coming generations of young doctors will curse us with fluency and justice. The public will probably not deserve what it will get, but it will suffer no less for that. It is not necessary for this to occur, if we will ourselves take a hand in our future, if we are honest and apply to the formation and management of this service the same spirit with which we approach our professional work. There is no need to be wedded to the scheme I proposed to the profession recently. Myself I like it because it is thorough and complete and does seem to me to cover most of the essentials. The same results may be attainable in other ways. What is necessary is that medical men should cease to allow the apparent security of the *status quo* to dazzle their eyes, and should make an earnest study of the best methods of applying medical science to medical needs. There are certain essentials which must be fulfilled by any good medical service. One of them is the abolition of the financial relationship now existing between a doctor and his patients. That I know is a radical change, but in my opinion it is an essential condition of any thorough reform. A complete service must also provide for the proper distribution of doctors to places where their services are most required; it must provide for an even and regulated flow of trained men into the profession, and promise them reasonable comfort and leisure when they leave it; it must provide for the constant refreshing and reeducating of men throughout their working years in the latest advances in medical knowledge and treatment; it must abolish the conflict between preventive and curative medicine and link

these two branches in harmony for the benefit of the community; and it must ensure that men of ability and high ethical standard are satisfied to enter the service and work in it, and that they should be anxious to see their own sons enter it after them. There may be many ways of achieving these objects, but no plan which does not comprehend them all can be considered a good or complete one.

It will not make perfect doctors. With the best of construction and the wisest of management, some feeling of impersonality in working for a salary and as part of an organization will have to take the place of the present urge for personal and individual success, and no one can forecast how that change of motive will affect any particular man. In our present system there are enough men whom the struggle for personal success seems to spoil rather than improve, to make one feel that the average will probably be not much different from what it is now. But the conditions under which they work will be altered, and surely for the better. Quoting again from the same source as my text: "If a State scheme will give the doctor more equipment, more medical help, and better surroundings, and more time for each patient, then if that man is a real doctor, he cannot say with truth that the State has hindered him in being what he professed to be." Second-rate men will always exist in any system, as they do now in our present one. Where at present the second-rate man commonly discards the ambitions and ideals instilled into him in his training school when he enters the economic arena, and attempts to make his bid for success by short cuts and easy paths to popularity; in the new system the similar man may succumb to the temptation to sit back on his assured salary and do as little work as is compatible with his continuing to draw it. Such men are a danger to, and a blight on, any system, however devised; and that fact in itself constitutes the greatest reason for us professional men to see that as few as possible of the type are attracted into the new service. We must try to have it professionally devised, under professional control, with professional supervision, and, above all, filled with the professional spirit.

That is the freedom which the medical profession must fight to retain; no other is worth the fight. And I am afraid that the time is becoming comparatively short for us, and that we have now no more than sufficient time at our disposal to lay our plans for the fight to retain it.

Let me restate my position.

I believe that changes both in our social structure and in medical science make it imperative that the whole of our present system of medical service should be reorganized in the interests of the community.

I believe that there is an imminent danger that the reorganization may be introduced in piecemeal and politically inspired forms which may well have a very disastrous effect on the public welfare as well as on the medical profession.

I believe that our main hope for the future lies in our own recognition and acceptance of the need for reform, and in our own preparation of a complete and concrete plan which will forestall less well-instructed attempts.

I am aware that most likely there will be something to regret in the passing of the old-style general practitioner, even as there has been in the passing of the old-style individual craftsman in industry, but I believe that none the less the sacrifice is necessary and is demanded of us.

And I believe finally that what is lost can be made very much less and that what is valued and valuable in our present system can be carried over into the new order in very much greater degree if we will ourselves prepare and organize the change.

In that way we shall contribute our small share in the much vaster social reorganization which, all statesmen tell us, is to come into being with peace, and which is to make this war worth while fighting. And in that way too we shall best retain that freedom for the execution of our wish and desire to make a good job of that to which we have set our hands.

THE ISO-AGGLUTININ TITRE OF POOLED SERUM OR PLASMA.[1]

By RACHEL JAKOBOWICZ and LUCY M. BRYCE,
Melbourne.

IN view of its practical advantages over whole blood, particularly for certain war purposes, the use of stored serum or plasma for therapeutic transfusion is receiving considerable attention at the present time.

It has been generally accepted that serum or plasma may safely be given without knowledge of the recipient's blood group or preliminary cross-matching tests. This view would seem to be based, first, on the fact that in the large majority of cases in which the blood of so-called "universal donors" of group O is given to recipients of other groups, the agglutinins present in the introduced serum do not cause harmful reactions, and secondly, on recent reports[1][2] of the use of serum or plasma without untoward effects.

The absence of clinically obvious harmful effects of reactions between the introduced agglutinins and the recipient's agglutinogens is generally attributed to adequate dilution. This may be the correct explanation in some cases, as the introduced serum, in an average transfusion, approximates in volume to only one-twentieth of that of the recipient. As, however, the majority of specimens of serum when tested *in vitro* have agglutinating activity in considerably higher dilutions than one-twentieth,[3] it seems likely that when serum of unknown but high titre is given, the degree of dilution may not be sufficient to prevent reactions.

An experiment by Levine and Mabee[4] illustrates this point. They mixed, *in vitro*, one part of citrated group O blood with nine parts of group A blood, this being the average ratio between the volumes of the blood of donor and recipient in transfusions. The mixtures were examined microscopically. In most of their cases no agglutination occurred; but with one sample of group O blood there was strong agglutination of approximately nine-tenths of the red cells present (that is, those representative of the recipient). Levine and Mabee concluded that persons possessing such serum must be regarded as potentially "dangerous universal donors".

Hesse,[5] in an analysis based on answers to a *questionnaire* of 217 cases of "hæmolytic shock" (with 56% mortality rate), found that the majority were due to errors in blood group tests, but that 46 followed the use of "universal donors". It is not stated in the reviews of this work from which we quote these figures (the original article not being accessible) whether these 46 reactions could be correlated with any definite causal factors; but according to Hesse they are most likely to occur if more than 200 cubic centimetres of blood are given, if the recipient is very anæmic, or if the donor's serum has a high agglutinating titre.

There are many other clinical reports describing hæmolytic reactions after the use of "universal donors". In some of these, retests after the event revealed a high agglutinating titre in the donor's serum, or agglutination by factors other than the two major iso-agglutinins, while in others the explanation is not clear. It may be noted that it is often difficult to obtain definite evidence concerning the possible causal factors in individual transfusion reactions, and hence to assess their relative significance in a sufficiently large series; this is partly on account of their comparative rarity, and partly because even if the necessary laboratory facilities are available, blood from the donor, or suitable samples of the blood of the recipient, particularly that taken before the transfusion, may not be available for a retest.

Whatever factors are responsible, however, the frequency of severe reactions following the use of "universal donors" is less than would be expected if dilution of the introduced agglutinins were the only factor responsible for their apparent inactivity in the recipient's blood. Ottenberg[6]

[1] From the Walter and Eliza Hall Institute, Royal Melbourne Hospital, and the Blood Transfusion Service of the Victorian Division of the Australian Red Cross Society.

as early as 1911 made some interesting observations on this point. He concluded, as a result of his *in vitro* experiments, that, except in cases of severe anæmia, there would be an excess of red cells in the recipient's blood in relation to the donor's agglutinins. This would result in complete absorption, but also in such wide dispersal of the agglutinins that there would be insufficient per cell to effect more than minor degrees of agglutination, often visible only microscopically. He also considered that such small aggregates (perhaps only of four or five cells) would block only peripheral capillaries, and thus be relatively harmless. It is relevant to note that the majority of persons whose blood contains the red cell agglutinogens A and B (that is, those of groups AB, A or B) have also receptor substances of similar group specificity in other tissues and body fluids, including serum. Wiener[7] points out that absorption by these receptor substances will also tend to neutralize the introduced agglutinins.

Although, therefore, it is recognized that dangerous reactions from the agglutinins present in serum are infrequent, they may be sufficiently serious to warrant attempts to prevent their occurrence.

The possibility that agglutinins can be removed during the preparation of plasma or serum by pooling of blood of different groups has recently received attention. Thus Edwards, Kay and Davie[9] point out that if samples of blood containing the factors A and B are mixed, reduction is effected in the agglutinating titre of the resulting plasma. They rightly attribute this reduction to reciprocal absorption of the agglutinins by the red cell agglutinogens, which, if present, would undoubtedly cause such absorption. We considered, however, in view of the existence of group-specific receptor substances in serum (referred to above), that a similar reduction might occur, even if, as is the practice here, the pooling is made after the cells have been removed. We have therefore investigated quantitatively the degree of reduction of titre produced by mixtures of known quantities of serum or plasma from blood of different groups.

At the time when this work was commenced, we were not aware of any similar quantitative studies. Since then, a paper on "Suppression of Iso-agglutinins", by S. O. Levinson and A. Cronheim,[2] of Chicago, has come to hand. They, however, while recognizing and stressing the practical significance of pooling, demonstrate only the interaction of individual samples of serum of group A and B, and do not show quantitatively the results of the mixture of several samples of blood.

Material and Technique.

The samples of serum examined have all been obtained from voluntary donors of the Red Cross Blood Transfusion Service.

Donors whose blood is used for preparation of serum are asked to avoid fatty foods in the breakfast or lunch prior to the bleeding. The pooled batches so far examined have each been composed of samples of blood taken on the same day, but the method of preparation has differed in the batches referred to as "serum A" and "serum B".

"Serum A" is the pooled serum prepared at the Walter and Eliza Hall Institute for therapeutic use and clinical study at the Royal Melbourne Hospital. The method adopted is to allow the blood of each donor to clot separately. The serum available is then withdrawn, measured, and pooled in amounts of 500 cubic centimetres. Small samples of blood from each donor are set aside at the time of bleeding. The serum from these is kept in the refrigerator till a similar sample is available from the pooled product, when the agglutinin titres of individual and pooled samples are estimated with the same red cells.

"Serum B" is the pooled serum prepared at the Commonwealth Serum Laboratories for military use. At the time of bleeding small samples are retained without admixture with anticoagulant for estimation of individual agglutinin titres. The main bulk of the blood from each donor is mixed during withdrawal with potassium oxalate (nine cubic centimetres of a 10% solution to 600 cubic centimetres of blood). The red cells are removed by centrifugalization and the individual yields of plasma are pooled. The theoretical amount of calcium chloride (14·5 cubic centimetres of specific gravity of 1,022 to 300 cubic centimetres of plasma) is added to promote clotting. In three cases, small samples of the plasma from each donor were retained, and serum was prepared from them individually by Miss May Kennedy, so that the agglutinin titre at different stages of the preparation could be estimated. No significant difference was found between the titre of the original serum obtained by direct clotting of whole blood, the plasma, or the serum obtained from it in the absence of the blood cells.

Estimations of iso-agglutinin titre were made by mixture, in small tubes (approximately eight millimetres' internal diameter), of serial doubled dilutions in normal saline solution of the serum to be tested, with an equal volume of a 1% suspension of red cells of appropriate group, of known average sensitivity, and withdrawn from the donor not more than twenty-four hours prior to the tests.

Readings were made after two hours at room temperature on samples of the mixtures which for ease of comparison had been transferred from the tubes to "army tiles".[3] Agglutination just visible to the naked eye was recorded as "+", and the reciprocal of the dilution in which this occurred was usually taken as the titre. If, however, finer agglutination, visible with a hand lens, was present in the next serial dilution, the latter was recorded as "±", and an interpolated figure, usually the reciprocal of the dilution midway between those giving readings of "+" and "±", was recored as the titre.

The composition of 14 batches of pooled serum which we have examined is shown in Table I.

Results.

In each case calculations have been based on the relative amounts and titres of the constituents of the pooled samples, and the degree of dilution of the anti-A and anti-B agglutinins effected by the specimens of serum from which these were absent. The figures obtained are recorded as the calculated titre of the pooled sample, and compared with those obtained by titration (the "observed titre"). In the case of "serum B", the slight diluting effect of the added potassium oxalate and calcium chloride has been disregarded.

As an example of the calculations made, it will be seen (from the figures given in Table I) that in Batch I of pooled serum:

the relative strength of the anti-A agglutinin

in serum (12) is	200×16 =	3,200
(13) is	210×48 =	10,080
(15) is	230×64 =	14,720
	640	28,000

and of anti-B agglutinin

in serum (3) is	250×8 =	2,000
(4) is	190×16 =	3,040
(15) is	230×96 =	22,080
	670	27,120

Therefore the anti-A titre of specimens (12), (13) and (15) mixed should be $\frac{28,000}{640} = 44$, and the anti-B titre of specimens (3), (4) and (15) mixed should be $\frac{27,120}{670} = 40$. But the total volume of pooled sample = 1,280 cubic centimetres. Therefore mixture of (12), (13) and (15) is only $\frac{640}{1,280}$ of the total and mixture of (3), (4) and (15) is only $\frac{670}{1,280}$ of the total. Therefore the anti-A titre of the whole will be reduced by dilution to $\frac{640}{1,280}$ of 44 = 22, and the anti-B titre of the whole will be reduced by dilution to $\frac{670}{1,280}$ of 40 = 21. That is, the calculated titres are: anti-A, 22; anti-B, 21. But the observed titres were: anti-A, 8; anti-B, less than 2.

TABLE I.

Composition of Pooled Batches of Serum.

Batch of Pooled Serum.	Group, Amount and Agglutinin Titre of Constituent Blood Samples.																	
		AB.		A.									B			O.		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
I (A)[1]	Amount (cubic centimetres).	200		250	190								200	210		230		
	Titre	—		8	16								16	48		α^2: 64, β^4: 96		
II (A)	Amount (cubic centimetres).			210	250	100	170									250	170	
	Titre			128	32	8	64									α: 64, β: 64	α: 32, β: 64	
III (A)	Amount (cubic centimetres).	160		140	280								260	220				
	Titre	—		2	16								32	8				
IV (A)	Amount (cubic centimetres).			260	230								220					
	Titre			12	12								96					
V (A)	Amount (cubic centimetres).	200		210	150	240							220					
	Titre	—		48	64	32							32					
VI (B)[1]	Amount ..			1 pt.	1 pt.	1 pt.							1 pt.			1 part	1 part	
	Titre			16	64	4							32			α: 96, β: 48	α: 128, β: 96	
VII (B)	Amount ..			1 pt.	1 pt.	1 pt.										1 part	1 part	
	Titre			8	64	16										α: 128, β: 48	α: 96, β: 64	
VIII (B)	Amount ..	1 pt.		1 pt.	1 pt.	1 pt.							1 pt.			1 part	1 part	
	Titre	—		32	64	16							48			α: 64, β: 8	α: 64, β: 32	
IX (A)	Amount (cubic centimetres)			270	100	170	100	200					190	260	200	220		
	Titre			16	8	14	14	14					64	16	32	α: 384, β: 32		
X (A)	Amount (cubic centimetres).			180	250	100	80	190	180	170	180	120	250	250				
	Titre			8	32	96	128	96	48	24	128	24	96	48				
XI (B)	Amount (cubic centimetres).	320		340	300	350	305	325	320				350	340	190	310		
	Titre	—		48	16	128	8	24	12				128	128	32	α: 64, β: 48		
XII (B)	Amount (cubic centimetres).	350	350	350	260	350	350	350	350	350						350	350	
	Titre	—		16	24	8	64	14	32	48						α: 32, β: 16	α: 64, β: 32	
XIII (B)	Amount (cubic centimetres).	60		320	340	230	325	310	320	350	320	340	315	330	340			
	Titre	—		32	8	64	6	16	16	96	8	32	128	128	64			
XIV (B)	Amount (cubic centimetres).	350		140	170	330							270			360		
	Titre	—		32	32	48							64			α: 128, β: 96		

[1] A = pooled "serum A". [2] B = pooled "serum B". [3] α = Anti-A agglutinin. [4] β = Anti-B agglutinin.

A summary of the results obtained by similar calculations in respect of the 14 illustrative batches described in this paper are shown in Table II.

It will be seen from the figures shown in Table II that in almost every case the actual titre of the pooled product is substantially less than would be expected if the degree of dilution present were the sole factor responsible for its reduction. It will be noted, however, that in Batches II and VII no significant reduction occurred in respect of the anti-B titre. This may be attributable to the absence

TABLE II.

Difference between Calculated and Observed Titre in Pooled Serum.

Batches of Pooled Serum or Plasma.	Number of Specimens of Serum of Each Blood Group in Pooled Batches.						Anti-A Titre.		Anti-B Titre.	
	Group AB.	Group A.			Group B.	Group O.	Calculated.	Observed.	Calculated.	Observed.
		Subgroup A_1.	Subgroup A_2.	Subgroup not Known.						
I	1	—	—	2	2	1	22	8	21	8
II	—	1	—	3	—	2	18	2	66	64
III	1	—	—	2	2	—	10	<2	4	<2
IV	—	2	—	—	1	—	30	2	8	<2
V	1	—	2	1	1	—	6	4	27	8
VI	—	1	—	2	1	2	38	<2	37	8
VII	—	—	—	3	—	2	51	16	44	48
VIII	1	1	—	2	1	2	25	8	25	8
IX	—	1	—	4	3	1	61	6	11	<2
X	—	1	—	8	2	—	16	4	48	12
XI	1	2	—	4	3	1	25	3	25	6
XII	2	3	—	3	—	2	11	2	24	6
XIII	1	2	—	6	3	—	24	3	23	3
XIV	1	—	—	3	1	1	39	12	34	6

of any group AB or B blood from these batches, and hence the absence also of specific receptors capable of interaction with the anti-B agglutinins.

An experiment designed to ascertain whether in serum devoid of specific receptor substances there are other elements with reducing action was carried out as follows:

A specimen of group O serum (which contains no specific receptors for anti-A and anti-B agglutinins) was absorbed with A and B cells till all its agglutinins were removed; as a control, a specimen of group A serum was similarly absorbed with B cells. These specimens were used as diluents for the titration, with group A cells, of a specimen of group B serum, and the results were compared with a similar series of dilutions of the latter in normal saline solution, as shown in Table III.

It therefore appears that serum which has no specific receptor substances behaves like normal saline solution, only as a diluent, whereas group A serum, in which these substances are present, reduces appreciably the anti-A titre of the group B serum.

From Table II it may also be noted that in Batch VII, in addition to the absence of reduction of the anti-B agglutinins already referred to, there is less reduction of the anti-A agglutinins than in the majority of cases. This finding may possibly be accounted for by the fact that both the specimens of O serum present in this batch were of high titre (that is, 128 and 96 respectively); it is possible also that one or more of the three constituent specimens of group A blood belonged to subgroup A_2.

Thomsen[10] and many other observers have shown that the red cells, tissues and body fluids of persons belonging to the subgroup A_2 have far less absorptive power for anti-A agglutinins than those of subgroup A_1. It was therefore thought possible that if some or all of the group A components of a pooled batch belonged to this subgroup, there might be less reduction of the anti-A titre than in batches containing only subgroup A_1. The following experiment was therefore carried out:

Specimens of group B (anti-A) serum were mixed with equal volumes of normal saline solution and of serum from subgroups A_1, A_2, and A_1 and A_2 pooled. The four mixtures were allowed to stand for two hours at room temperature, so that absorption of agglutinins could occur. Their anti-A titres were then estimated.

The results (shown in Table IV) indicate that considerable reduction has been effected by serum of subgroup A_1, none by that of subgroup A_2, and an intermediate amount by the mixture containing both A_1 and A_2.

TABLE IV.

Relative Reducing Action of Serum of Subgroups A_1 and A_2.

Group B Serum.	Dilutions of Serum Mixtures.			
	1/4	1/8	1/16	1/32
After two hours' contact with:				
Normal saline solution	+++	++	+	±
Serum of subgroup A_1	++	+	–	–
Serum of subgroup A_2	+++	++	+	±
Pooled serum of subgroups A_1 and A_2	++	+	+	–

There may also be variation in the interaction between group B serum and the receptors in group A serum referable to individual differences in the former. Thus in one sample of group B serum (number 13 in Batch X shown in Table I) the anti-A titre was not greatly reduced by mixture with any of nine samples of group A serum, all of which caused definite reduction of the anti-A titre of the other sample of group B serum (number 12) included in this batch. The significance of these variations (shown in Table V) is doubtful. Further investigation is necessary

TABLE III.

Diluent.	Dilution of B Serum.					
	1/4	1/8	1/16	1/32	1/64	1/128
Normal saline solution ..	+++	+++	++	+	+	–
Absorbed O serum	+++	+++	++	+	+	–
Absorbed A serum	+++	++	+	–	–	–

TABLE V.

Difference between Reduction of Titre in Two Samples of Group B Serum.

——	Samples of B Serum.	Dilution of Group B Sera.					
		1/4	1/8	1/16	1/32	1/64	1/128
Titration with normal saline solution	Batch X, number 12	+++	+++	+++	++	+	±
	Batch X, number 13	+++	++	++	+	±	—
After absorption with A serum— Batch X, number 3 ..	Batch X, number 12 ..	+++	++	+	–		
	Batch X, number 13	–	–	–	–		
Batch X, number 4 ..	Batch X, number 12	+++	++	+	±	–	
	Batch X, number 13	–	–	–	–	–	
Batch X, number 5 ..	Batch X, number 12	+++	+++	++	+	–	
	Batch X, number 13	±	–	–	–	–	
Batch X, number 6 ..	Batch X, number 12	+++	+++	++	+	–	
	Batch X, number 13	+	+	–	–	–	
Batch X, number 7 ..	Batch X, number 12	+++	++	++	±	–	
	Batch X, number 13	+	±	–	–	–	
Batch X, number 8 ..	Batch X, number 12	+++	+++	++	+	±	
	Batch X, number 13	±	–	–	–	–	
Batch X, number 9 ..	Batch X, number 12	+++	++	+	±	–	
	Batch X, number 13	±	–	–	–	–	
Batch X, number 10 ..	Batch X, number 12	+++	++	+	±	–	
	Batch X, number 13	±	–	–	–	–	
Batch X, number 11 ..	Batch X, number 12	+++	++	+	±	–	
	Batch X, number 13	±	–	–	–	–	

to ascertain their nature and frequency, and hence the extent to which they may effect reduction of anti-A titre by pooling.

Reduction of Titre by Addition of Saliva.

Many investigators, whose work is quoted by Wiener,[8] have shown that saliva may contain group-specific receptor substances in high concentration. It is therefore possible (as shown in Table VI) to effect suppression of agglutinins from serum by the addition of saliva which has been boiled, in order to sterilize it and to destroy enzymes which may interfere with its absorptive power.

It has been shown by Schiff and Sasaki[11] that certain persons, irrespective of blood group, have an hereditary inability to "secrete" specific receptor substances, and it is known also that those belonging to subgroup A_2 have saliva relatively poor in these substances. Provided therefore that saliva from persons of these two categories is not selected, it would be theoretically sound to use it as a means of suppressing agglutinins. It is doubtful, however, whether such a procedure would be acceptable to those responsible for the preparation of serum or plasma for therapeutic use.

An experiment which illustrates the powerful absorptive action of a sample of boiled saliva from a person belonging to blood group B on the anti-B agglutinins present in serum of group A, and as a contrast the complete lack of absorption of these agglutinins by a sample of saliva from a person belonging to blood group A, was carried out in the following manner:

Small quantities of the serum were mixed with equal volumes of a series of dilutions in normal saline solution of the saliva of each group and allowed to stand for two hours at room temperature. Serial doubled dilutions in saline solutions of these mixtures and of a control mixture of equal volumes of the specimens of serum and normal saline solution were titrated with red cells of group A.

The results are shown in Table VI.

Discussion.

When preparation of pooled serum for storage was first undertaken in Melbourne, efforts were made to supply for this purpose only donors belonging to group AB, or those of other groups known to have low agglutinin titres (of 20 or less). As such persons form, however, a relatively small proportion of the population,[9] and as some of the most readily available and experienced donors had been enrolled before the adoption in 1939 of estimation of agglutinin titre as part of the routine examination of Red Cross donors, increasing demands made it difficult to secure the requisite number of individuals with known low agglutinin titre. Tentative trials were therefore made of the effect of introducing one or more specimens of serum of higher titre into each batch. The encouraging results led to the more detailed study presented in this paper. Similarly, the opportunity has been taken to study the effect of the use of blood of subgroup A_2, possibly introduced from donors classified before the institution of subgroup tests as a routine procedure.

Since clinical observation indicates that pooled serum or plasma of unknown titre may be given without harmful effects, the necessity for active measures to eliminate agglutinins is still debatable. Diminution of the original agglutinating titre will almost certainly occur if storage is maintained over a period of months, particularly if the serum or plasma is kept in liquid form, and at temperatures above 0° to 2° C.

Nevertheless, it is possible to envisage circumstances in which it may be advisable to take active measures to ensure a low agglutinin titre in stored serum. For instance, the examination of a sample of dried serum carried out by us showed that the original titre of 96 was present in the redissolved product. If dried serum of unknown titre is used in higher concentration than its original volume, a procedure sometimes adopted, there is obvious danger of the introduction of concentrated agglutinins capable of acting on the recipient's red cells.

Even if liquid serum, or dried serum restored to its original volume, is used, the amount given in a transfusion of, say, 500 cubic centimetres will be often approximately double that of the serum given in a transfusion of a similar amount of whole blood. It is possible therefore that further observation of larger series of serum or plasma transfusions may show a greater incidence of reactions attributable to agglutination of recipients' red cells than has been caused by the widespread use of "universal donors" for whole blood transfusions. On theoretical grounds, it may be wise not to include group O blood of high or unknown titre in pooled samples, as this group contains both anti-A and anti-B agglutinins, but no specific receptor substances. Conversely, the blood of group AB (especially subgroup A_1B) is particularly suitable for inclusion, as it possesses receptors capable of interaction with both anti-A and anti-B agglutinins. The rarity of this group, however, makes it a relatively unimportant factor in any large-scale preparation of stored serum.

It is possible that, in times of military stress, available supplies of serum will be used so rapidly that the diminution in titre caused by the efflux of time may not occur.

Finally, it appears that there may be exceptions to the general rule that absorption of agglutinins will always be readily effected by reciprocal receptor substances to the extent anticipated, as in the case of a group B serum described above, and of group A blood of unknown subgroups. In the present state of our knowledge, the most practical method of overcoming such irregularities would seem to be the pooling in one batch of as many individual samples of blood as possible (particularly of groups AB, A and B). The determination of the agglutinin titre of the final product seems advisable as a control on the effectiveness of the pooling.

TABLE VI.

Absorption of Serum Agglutinins by Saliva.

Mixtures Allowed to "Absorp" for Two Hours.	Titre of Serum after Two Hours' Absorption.					
	4	8	16	32	64	128
0·1 cubic centimetre serum A + 0·1 cubic centimetre saline solution	+++	+++	+++	+++	++	+
0·1 cubic centimetre serum A + 0·1 cubic centimetre saliva A in dilutions ½ to 1/128	+++	+++	+++	+++	++	+
0·1 cubic centimetre serum A + 0·1 cubic centimetre saliva B in dilutions 1/8 to 1/128	+	–	–	–	–	–
0·1 cubic centimetre serum A + 0·1 cubic centimetre saliva B diluted 1/256	±	–	–	–	–	–
0·1 cubic centimetre serum A + 0·1 cubic centimetre saliva B diluted 1/512	+	–	–	–	–	–
0·1 cubic centimetre serum A + 0·1 cubic centimetre saliva B diluted 1/1024	++	+	±	–	–	–

Summary and Conclusions.

1. The effect of "pooling" on the iso-agglutinin titre of human serum has been studied quantitatively.

2. It has been found that the mixture of samples of serum from blood containing both A and B factors results in reciprocal suppression of the anti-B and anti-A agglutinins to an extent greater than can be accounted for by dilution.

3. It has been shown that this reduction of titre is due to the presence of receptor substances of similar group specificity to the red cell agglutinogens; it is therefore not effected by serum of blood belonging to group O, in which red cell agglutinogens and group-specific receptor substances are absent, and relatively little by that of subgroup A_2, which is characterized by agglutinogens of less avidity for anti-A agglutinins than those of subgroup A_1.

4. The agglutinins in certain specimens of group B serum are not absorbed by group A serum to the extent anticipated.

5. The use for transfusion of serum (rather than whole blood) may increase the likelihood of reactions between introduced agglutinins and recipient's red cells. A low agglutinin titre is therefore desirable in pooled serum.

6. A practical means of ensuring this desideratum is to include in each pooled batch many individual samples of serum from blood of groups AB, and A and B, and to limit the use of serum from group O blood, particularly if it is of high or unknown titre. An alternative method of reducing agglutinin titre by mixture with suitable samples of boiled saliva is also discussed.

Acknowledgements.

We wish to thank Major S. W. Williams, Captain E. B. Drevermann, of the Australian Army Medical Corps, Miss Marjorie Bick, M.Sc., of the Walter and Eliza Hall Institute, and members of the staff of the Commonwealth Serum Laboratories, particularly Miss May Kennedy, for their cooperation in supplying us with the samples of blood and serum.

References.

(1) M. M. Strumia, J. A. Wagner and J. F. Monaghan: "The Use of Citrated Plasma in the Treatment of Secondary Shock", *The Journal of the American Medical Association*, Volume CXIV, 1940, page 1337.

(2) S. O. Levinson and A. Cronheim: "Suppression of Iso-Agglutinins", *The Journal of the American Medical Association*, Volume CXIV, 1940, page 2097.

(3) L. M. Bryce and R. Jakobowicz: "The Estimation of the Iso-Agglutinin Titre of Human Serum and Its Practical Applications", THE MEDICAL JOURNAL OF AUSTRALIA, 1941, in the press.

(4) P. Levine and J. Mabee: "A Dangerous Universal Donor Detected by the Direct Matching of Bloods", *The Journal of Immunology*, Volume VIII, 1923, page 424.

(5) E. Hesse, quoted by A. S. Wiener, *loco citato*, page 92.

(6) R. Ottenberg: "Studies in Iso-agglutination", *The Journal of Experimental Medicine*, Volume XIII, 1911, page 425.

(7) A. S. Wiener: "Blood Groups and Blood Transfusion", second edition, 1939, page 49.

(8) A. S. Wiener: *Loco citato*, page 187.

(9) F. R. Edwards, J. Kay and T. B. Davie: "The Preparation and Use of Dried Plasma for Transfusion", *The British Medical Journal*, Volume I, 1940, page 377.

(10) O. Thomsen and V. Friedenreich: *"Méthode élémentaire pour la détermination des groupes sérologiques A et A^1 (groupes AA^1 et AA^2 de Landsteiner) chez l'homme", Comptes rendus de la Société de biologie*, Volume CIII, 1930, page 1301.

(11) F. Schiff and H. Sasaki: *"Ueber die Vererbung des serologischen Ausscheidungstypus", Zeitschrift für Immunitäts-forschung und experimentelle Therapie*, Volume XXXVII, page 129.

EXPERIMENTAL MEASLES: TRANSMISSION OF THE DISEASE TO MONKEYS, FAILURE TO TRANSMIT MEASLES TO RABBITS, CULTIVATION OF THE VIRUS ON THE CHORIO-ALLANTOIC MEMBRANE.[1]

By E. WESTON HURST and BARBARA COOKE.

(From the Institute of Medical and Veterinary Science, Adelaide, South Australia.)

IN the summer of 1939-1940, and particularly between the end of October and the middle of February, measles was very prevalent in South Australia; over 8,000 cases occurred in slightly more than three months. We attempted to grow the virus on the chorio-allantoic membrane of developing hens' eggs. Unfortunately, in the hot months our usually reliable source of fertile eggs, the Parafield Poultry Station, supplies eggs of very low fertility. When the epidemic was at its height we could not obtain eggs with a fertility rate of more than about 20%, while many eggs at first developing normally died spontaneously after a week or ten days. In only a few cases, therefore, was it possible to inoculate eggs directly with human material. We transmitted the disease serially in monkeys, however, and initiated egg cultures with blood or tissue suspensions of infected animals. In the course of the work with monkeys we confirmed the findings of previous workers, and also made a number of new observations. We were unable to transmit the disease to rabbits. The work came to a standstill because the supply of monkeys was exhausted; further deliveries were retarded by conditions arising out of the war. When monkeys were again available the epidemic was almost past, and attempts to transmit the disease were fruitless.

Results of Primary Inoculations in Animals.

Nasal washings or blood, or both, were collected from patients in the pre-eruptive or early eruptive stages of measles. Diagnosis in the cases observed in the pre-eruptive stages was confirmed later; a few suspicious cases in which a rash failed to develop subsequently were omitted from consideration. Blood was defibrinated by being shaken with glass beads. The nasal washings with 20 to 30 cubic centimetres of physiological saline solution were taken immediately to the laboratory, shaken vigorously for a few minutes to break up plugs of mucus, and centrifuged for five minutes at a speed of about 3,000 revolutions per minute. The supernatant fluid was passed through Berkefeld N candles previously "lined" with broth. The bacteriologically sterile filtrates were mixed with the blood (if taken) and used for intramuscular, intravenous or intratesticular inoculation of monkeys or rabbits. When eggs were inoculated, blood and filtered nasal washings were used separately. Filtrates of nasal washings were also inoculated into the trachea of monkeys or rabbits. The centrifuged but unfiltered washings were sometimes sprayed with an atomizer into the noses of monkeys under ether anæsthesia. At the time of inoculation, the hair was removed with electric clippers from the chest and abdomen. The monkeys were kept in a number of isolation units to minimize the risk of infection by contact.

Table I shows that when the epidemic was at its height our attempts at transmission from man to monkeys met with considerable success. As will be seen shortly, there was some reason to believe that those monkeys failing to react belonged to species naturally refractory, or else to batches immune as a result of previous contact with the virus. On the other hand, rabbits consistently failed to show any signs of infection.

Infection in the Monkey.

Since doubt has been expressed as to the suitability of the common rhesus monkey for experimental transmission of measles, we used a number of different species, particularly for the primary inoculations from human cases. The results obtained at the height of the epidemic are summarized in Table II and are amplified below.

Macacus mulatta.—Of nine rhesus monkeys inoculated with material from human patients, six gave clearly positive results, while in two a doubtful infection resulted. Twelve of 18 passage animals were successfully infected; the negative results were mostly in remote passages when the infection was tending to die out (see below) and reactions generally were much milder.

Macacus radiatus.—The only animals of this species available both gave reactions which were among the most pronounced encountered.

Macacus irus.—In the experiments listed in Table II, and in a number of others involving splenectomy prior to attempted infection, a clear-cut result was never obtained, even when a positive result was obtained by the injection of the same material into *Macacus mulatta*. The animals

[1] The expenses of this work were defrayed by a grant from the National Health and Medical Research Council.

TABLE I.

Results of Inoculating Material from Human Cases of Measles into Monkeys.[1]

Case.	Stage of Disease.	Material Collected.	Route of Inoculation.	Subject of Inoculation.	Result.
I ..	First day of rash.	Defibrinated blood and nasal washings.	Intramuscular + intranasal.	*Macacus mulatta.*	Positive.
II ..	First day of rash.	Nasal washings.		*Macacus irus.*	Negative.
III ..	Second day of rash.	Nasal washings.	Intramuscular + intratesticular + intranasal.	*Macacus radiatus.*	Positive.
IV ..	Rash just appearing.	Nasal washings.	Intramuscular + intranasal.	*Macacus maurus.*	Negative.
V ..	Pre-eruptive.	Nasal washings.			
VI ..	Rash just appearing.	Nasal washings.	Intramuscular + intratesticular + intranasal.	*Macacus mulatta.*	Positive.
VII ..	Pre-eruptive.	Defibrinated blood and nasal washings.			
VIII ..	First day of rash.	Nasal washings.	Intramuscular + intratracheal.	*Macacus mulatta.*	Positive.
IX ..	First day of rash.	Nasal washings.		*Cebus fatuellus.*	Positive.
X ..	Pre-eruptive.	Defibrinated blood and nasal washings.		Rabbits.	Negative.
XI ..	Pre-eruptive.	Defibrinated blood.			
XII ..	Rash just appearing.	Nasal washings.	Intravenous + intramuscular + intratracheal.	Rabbits.	Negative.
XIII ..	Rash just appearing.	Defibrinated blood and nasal washings.			
XIV ..	Pre-eruptive.	Nasal washings.			
XV ..	Rash just appearing.	Defibrinated blood and nasal washings.	Intramuscular + intratracheal.	*Macacus mulatta* (2).	Positive (2).
				Macacus sinicus.	Positive.
				Rabbits.	Negative.
XVI ..	Pre-eruptive.	Nasal washings.	Intramuscular + intratracheal.	*Macacus maurus.*	Negative.
XVII ..	First day of rash.	Nasal washings.		*Macacus mulatta.*	Doubtful.
XVIII ..	Pre-eruptive.	Defibrinated blood and nasal washings.	—	Eggs.	? Positive.
XIX ..	Pre-eruptive.	Defibrinated blood and nasal washings.	—	Eggs.	Negative.
XX ..	Rash just appearing.	Defibrinated blood and nasal washings.			
XXI ..	First day of rash.	Defibrinated blood and nasal washings.	Intramuscular.	*Macacus maurus.*	Negative.
				Cynopithecus niger.	Negative.
			—	*Macacus mulatta.*	Positive.
				Eggs.	Negative.
XXII ..	First day of rash.	Defibrinated blood and nasal washings.	Intramuscular. —	*Macacus mulatta.* Eggs.	Negative. Negative.
XXIII ..	First day of rash.	Nasal washings.	Intramuscular.	*Macacus mulatta.*	Negative.
XXIV ..	Rash just appearing.	Defibrinated blood and nasal washings.	—	Eggs.	Negative.
XXV ..	Second day of rash.	Nasal washings.	Intramuscular. —	*Macacus mulatta.* Eggs.	Negative. Negative.
XXVI ..	Rash just appearing.	Nasal washings.	Intramuscular. —	*Macacus mulatta.* Eggs.	Negative. Negative.

[1] Cases I to XXI were obtained at the height of the epidemic, Cases XXII to XXVI when the epidemic had almost disappeared. Four of five monkeys inoculated with material from Cases XXII to XXVI were subjected to splenectomy.

came in three different consignments; with regard to two of these, the possibility of contact with a case of measles while in Adelaide could be excluded. As will be related, however, one batch suffered from latent malarial infections activated by splenectomy; these vitiated the experimental results.

Macacus maurus.—In the experiments listed in Table II, and in several involving prior splenectomy, no definite infection resulted. The monkeys belonged to two consignments, one resident in Adelaide for several years, and one arriving immediately before the experiments in question.

Cynopithecus niger.—This monkey was born in Adelaide, but had no closer or longer contact with the general public than had many of the rhesus monkeys giving positive results. It was about a year old at the time of the experiment, and failed to respond to the injection of material giving positive results in *Macacus mulatta*, though not in *Macacus maurus*.

Cebus fatuellus.—One animal gave a definite though mild reaction.

It is difficult to believe that closely related species such as the various macaques may vary considerably in their susceptibility to measles, while very distantly related species of South American monkeys (*Cebus fatuellus*) may be infected. Nevertheless, our results in a limited series of monkeys suggest that *Macacus mulatta* and *Macacus radiatus* are more suitable as laboratory animals than are their close relatives. No correlation could be established between the duration of stay of these monkeys in Adelaide, or their accessibility to the general public during an epidemic period, and their susceptibility to measles. An alternative explanation of the refractory state of some species might be found in their history prior to arrival in Australia.

TABLE II.

Results of Attempted Transmission of Measles to Various Species of Monkeys.[1]

Monkeys.	Primary Inoculations.	Results.	Attempted Passages.	Results.	Non-specific Deaths.
Macacus mulatta	9	6 Positive. 2 Doubtful.	18	12 Positive. 5 Negative.	2
Macacus radiatus	2	2 Positive.	—	—	—
Macacus irus	1	Negative.	1	Doubtful.	—
Macacus maurus	3	Negative.	2	Negative.	—
Cynopithecus niger	1	Negative.	—	—	—
Cebus fatuellus	1	Positive.	—	—	—

[1] The results are exclusive of animals subjected to splenectomy or to irradiation with X rays.

Serial passage was attempted in *Macacus mulatta* with three of the strains of virus isolated; for this purpose we inoculated intramuscularly defibrinated blood or suspensions of the spleen, liver and lymph glands of infected monkeys. The inocula were bacteriologically sterile. On passage the disease became progressively milder, and in each case died out at the fourth to sixth transfer.

Symptomatology.

It has been noted by others that monkeys infected with the virus of measles may exhibit only one of the several symptoms characteristic of the disease in man.

In the present series fever was present in all monkeys reacting at the first passage, in all but one at the second passage, and less constantly in subsequent passages. Of 20 monkeys showing evidence of infection, fever was present in 15; of the remaining five, all but one represented the third or fourth passage. The temperature of nearly all the animals had been recorded for at least several days prior to inoculation. The first rise of temperature occurred on the fourth to eleventh day after inoculation (three times on the fourth day, three times on the sixth, once on the seventh, three times on the ninth, twice on the tenth and three times on the eleventh day); generally, the longer periods of incubation were noted in the more remote passages. At its maximum the temperature attained a level of from 1° to 3·5° F. above the normal; most of the nigher temperatures were found in animals at the first and second passages. The rise of temperature lasted from two to five days, usually two or three days, and was sometimes followed by a period of greater daily variations than had occurred before infection. The peak of temperature was reached on the first to the fifth day, commonly on the first to the third day.

In seven monkeys at the first and second passages, of which several were infected by intramuscular injection of virus, cough was a prominent symptom and lasted for two to five days; in one case it was so pronounced that the animal was killed on the unfounded assumption that it was suffering from tuberculosis. In most animals the cough was first noticed one to five days after the first rise of temperature, but once it preceded fever by two days. However, since the monkeys rarely coughed when under direct observation, it was difficult to be certain of the exact times of appearance and disappearance of this symptom. At passages after the second, cough was not heard.

Owing to the time spent in examining patients and in collecting specimens in the suburbs, in the case of many of the earlier animals inoculated directly with human material it was not feasible to make regular counts of the leucocytes. In ten monkeys at the second and later passages the number of leucocytes fell on the fifth to the twelfth day. The normal number of leucocytes of different monkeys varied considerably and ranged usually from 7,000 to 16,000 per cubic millimetre; in some *Macacus maurus* monkeys numbers over 20,000 per cubic millimetre were frequent. (Similarly high counts are recorded by Blake and Trask,[1] Lucas and Prizer,[7] and Rake and Shaffer.[23]) In animals which contracted measles the number of leucocytes was reduced by 35% to 60% of normal and remained low for four to ten days. In three monkeys which had a pronounced fall in the number of leucocytes at the fourth or fifth passage there was no febrile reaction. In the remainder, the fall in leucocytes corresponded roughly with the first rise in temperature and lasted longer than did the febrile reaction. From this limited series of experiments it seemed that a fall in the number of leucocytes might denote successful transmission of the virus in the absence of any febrile reaction, and it is possible, therefore, that the number of positive cases recorded in the first part of Table I is understated.

Eight monkeys developed a rash, and four others were killed at a very early stage of infection; in the remainder no rash was noted. The rash appeared one or two days after the initial rise of temperature. In two animals at remote passages, a rash appeared in the absence of fever or of a drop in the number of leucocytes, while other monkeys inoculated with the same material (after splenectomy) showed these other signs of infection (see below). In six cases the rash took the form of deep red macules; in two it was maculo-papular. It was pronounced around the ischial tuberosities, in the groins and axillæ, and sometimes on the area from which hair had been clipped. It lasted for three to five days and faded sooner in the area first affected; there was no subsequent pigmentation.

After infection, two monkeys passed into a state of cachexia, from which one died on the twenty-first day after inoculation; this animal had been in the animal house for nearly a year and had previously withstood various experiments. Several monkeys suffered from diarrhœa during the febrile period. Two died with diarrhœa without showing definite symptoms of measles; these are recorded in Table II as non-specific deaths.

In seven tests, at times varying from four to thirteen days after inoculation, the blood was infective for fresh animals; in relation to the temperature, these times represented extremes of four days before the onset of fever and the third day of the febrile reaction. In two instances blood was still infective after being frozen for ten days at −10° C., but was innocuous after twenty-three days.

Immunity.

Seven tests with proved infective material gave negative results in monkeys having shown signs of infection twenty-four to thirty-six days previously. As the virus diminished in virulence with repeated passage, it became less and less suitable for use in immunity tests.

Effect of Splenectomy and of Irradiation with X rays on the Course of the Infection.

When it became apparent that the third strain of virus passed serially was tending to die out like the two preceding strains, we attempted to diminish the resistance of our animals prior to inoculation.

Five monkeys (*Macacus mulatta*) representing the third to the seventh passages were subjected to splenectomy immediately before receiving an intramuscular inoculation of blood and of a suspension of liver, spleen and lymph glands from infected animals. Four controls representing the third to the sixth passages received similar inocula without prior splenectomy. The results are shown in Table III. The splenectomy wounds healed without sepsis; in the first two days after the operation, the number of leucocytes sometimes rose slightly, to fall later. When fever occurred, the axillary and inguinal lymph glands were removed from four of the splenectomized animals to obtain material for passage. Although these later excisions were performed with the same care as were the initial operations, in every case sepsis ensued. Whether this was an effect of diminished resistance following splenectomy, of lowered resistance in the presence of infection with measles, or of disturbance to the local lymphatic circulation *et cetera*, could not be determined. Although the persistence of fever in these animals was perhaps due partly to this sepsis, the maximum temperature reaction was reached before excision of the glands, and there was no doubt that a greater response to infection was forthcoming in the animals subjected to splenectomy than in the controls. Thus a definite febrile reaction with a pronounced fall in the number of leucocytes was obtained at the seventh passage, whereas this virus and other strains had in untreated monkeys produced feeble reactions, or none at all, at passages earlier than the seventh. In animals whose wounds became septic, a rise in the number of leucocytes lagged for several days after it was obvious to the naked eye that the wounds were septic. Unfortunately at this point our supply of *Macacus mulatta* monkeys ran out, and we were left with only small groups of *Macacus maurus* and *Macacus irus*; in these, whether they had undergone splenectomy or not, we obtained no definite evidence of infection. After splenectomy several *Macacus irus* monkeys became seriously ill, and examination of blood films revealed hosts of malarial parasites; the animals ultimately died of this infection, of which there had been no sign prior to the operation.

Four monkeys (*Macacus mulatta*) were irradiated with X rays immediately before or after inoculation of known

TABLE III.

Effect of Splenectomy on Experimental Measles.[1]

Passage.	Normal Monkeys.	Splenectomized Monkeys.
Third.	No temperature reaction. Leucopenia fifth to tenth day; maximum drop from 12,000 to 5,000 per cubic millimetre.	Fever sixth to eleventh day (maximum rise 2° F. on ninth and eleventh days). Leucopenia sixth to fifteenth day (maximum drop 11,000 to 8,000 per cubic millimetre). Papular rash twelfth day. No excision of lymph glands.
Fourth.	No temperature reaction. Leucopenia fourth to seventh day; maximum drop from 11,000 to 5,500 per cubic millimetre.	Fever fifth to ninth day (maximum rise 2° F. on seventh day). Petechial rash ninth day. Excision of lymph glands seventh day. Sepsis apparent ninth day. Number of leucocytes constant until ninth day, then rose.
Fifth.	No temperature reaction. Leucocytes fell from 14,000 to 12,000 between fifth and tenth days.	Fever fifth to seventh day (maximum rise 1·5° F. on seventh day). Leucopenia fifth to thirteenth day; maximum drop from 12,000 to 7,500 per cubic millimetre. Excision of lymph glands seventh day. Sepsis apparent tenth day.
Sixth.	No temperature reaction. Leucocytes fell from 13,000 to 10,000 on eighth day only.	Fever seventh to tenth day (maximum rise 1·5° F. on seventh day). Leucopenia fifth to thirteenth day; maximum drop from 13,000 to 7,000 per cubic millimetre. Papular rash tenth day. Lymph glands excised eighth day. Sepsis apparent eleventh day.
Seventh.	——	Fever sixth to twelfth day (maximum rise 1·5° F. on sixth day). Leucopenia fifth to thirteenth day; maximum drop from 11,000 to 6,000 per cubic millimetre. Lymph glands excised seventh day. Sepsis apparent ninth day.

[1] Several control animals subjected to splenectomy alone had no rise of temperature and no leucopenia.

infective material. Three of these represented the third to the fifth passages of the strain mentioned above; the control group consisted of the animals listed in Table III and included both normal and splenectomized animals receiving similar material. The fourth, and a control not treated with X rays, represented the fifth passage of another strain of virus. The monkeys, confined in as small a space as possible, were irradiated for fifteen minutes in an open field at a distance of 50 centimetres from the source of rays; these were filtered through one millimetre of copper and one millimetre of aluminium. The current was 200 kilowatts at eight milliamperes. After irradiation the leucocytes fell to a level from one-sixth to one-quarter of normal; their number ranged from 4,500 to less than 2,000. Apart from the leucopenia, which could be attributed to the irradiation, none of the animals manifested any signs of infection, except for one which had a doubtful rise of temperature on the seventh day after inoculation. No evidence was obtained, therefore, that irradiation with X rays increased the susceptibility of the animals to measles.

Attempted Infection of Monkeys with Human Material in the Later Phases of the Epidemic.

In the later phases of the epidemic, when in South Australia only a hundred or so cases were occurring weekly, our attempts to transmit the disease to a new consignment of *Macacus mulatta* were fruitless (see second part of Table I). Four animals previously subjected to splenectomy, and one untreated animal, failed to respond by a rise of temperature or a fall in the number of leucocytes to the inoculations of presumably infective material. In a personal communication Dr. F. M. Burnet has pointed the analogy to the easy isolation of influenza virus during a major epidemic and the difficulty of isolating the virus from cases of clinical influenza during an inter-epidemic period.

Failure of the Virus to Survive in the Dried State.

Portions of the liver, spleen and lymph glands from several monkeys at the height of infection were frozen and dried *in vacuo* over phosphorus pentoxide. They were stored *in vacuo* over phosphorus pentoxide at a temperature of −10° C. When the material was tested for infectivity in monkeys from which the spleen had been removed, 152 to 294 days later, no infection resulted.

A Case of Probable Laboratory Infection with Measles.

Fourteen days after the peak of temperature in the third passage monkey of the second strain of virus passed serially, the assistant engaged in catching the monkeys and recording their temperatures developed a very extensive and almost confluent rash. For several days previously he had suffered from the usual premonitory symptoms of measles, and the diagnosis was further confirmed by Dr. A. R. Southwood, who was called into consultation. The temperature curve and leucocyte counts of the monkey are shown in Figure I; the animal suffered from cough between the thirteenth and sixteenth days, but did not develop a rash.

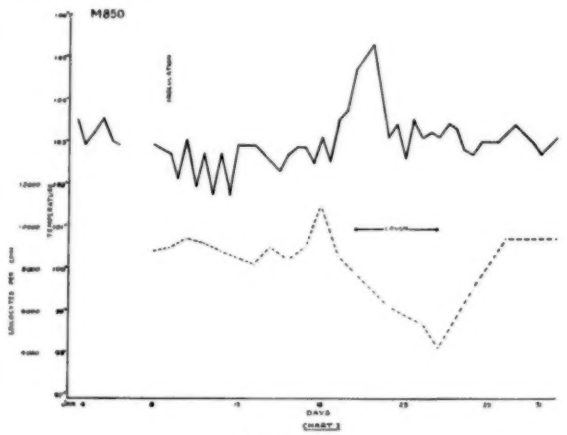

FIGURE I.

The assistant was a part-time university student of considerable intelligence, who was able to trace his movements exactly during the weeks preceding his illness. He had met few friends, none of whom suffered from any illness during the critical period; he himself had previously not contracted measles. From an isolated residence on the outskirts of the city he journeyed to the laboratory daily in the car of adult friends, all of whom remained quite well; in the evenings he returned in his father's motor car. He had visited a local cinema once, when he sat by himself in a very sparsely occupied gallery at a considerable distance from any other member of the audience. He had been in a public gathering once, at a parade of the Tenth Battalion; through the courtesy of Dr. J. M. Dwyer it was established that of the absentees from this and subsequent parades none suffered from measles. Going to and coming from the parade he had used a tramcar; the open structure of the parts of the Adelaide tramcars occupied by men (in Adelaide there is a fairly rigid segregation of the sexes) is not especially favourable for the dissemination of infection. It seems highly probable, therefore, that his infection had resulted from contact with the sick monkey.

This is Case XXI in Table I; the strain of virus which was isolated was the third to be passed serially in monkeys, and in animals from which the spleen had been removed (see above) was taken to the seventh passage.

Results of Inoculations into Rabbits.

Defibrinated blood and filtered nasal washings from three groups of human patients, two giving positive results and one not tested in monkeys, were injected into five rabbits. Material from three infected monkeys was administered to eight rabbits, four of which were subjected to splenectomy immediately before inoculation. The blood of some of these was transferred to nine rabbits in the course of two subsequent passages; blood was collected on the fourth to fourteenth day, and often a single animal received several samples taken at different times. Although the temperatures of the rabbits during the hot summer were more variable than were those of the monkeys, the rises always corresponded with periods of excessive external temperature; they were not accompanied or followed by leucopenia or rash. Thus no evidence was obtained that the rabbit is susceptible to measles. Owing to a shortage of animals we were unable to inoculate material from rabbits into monkeys.

Culture of Virus on the Chorio-Allantoic Membrane of Developing Hens' Eggs.

Eggs incubated for ten to thirteen days were inoculated by the technique of Burnet; the membranes were removed after a further three to five days at 37·5° C., usually four or five days. The results are summarized in Table IV. Six series of cultures were initiated with defibrinated blood or filtered nasal washings from human patients. Two series (5 and 8) were continuations of four of the preceding series (3 and 4, and 6 and 7 respectively); the members of each pair were merged after a number of transfers. Six series were initiated with blood or tissue suspensions, or both, of infected monkeys. The total number of passages varied from five to 30 before the cultures were finally discontinued. Although a proportion of the membranes at earlier passages were thickened and opaque, or showed minute separate opacities, these lesions appeared to be non-specific in nature and were insufficiently definite or constant to be of use in diagnosis.

When, after a variable number of passages, these cultures were inoculated into monkeys, suggestive reactions were twice obtained (numbers 1 and 2, and 10). The infection produced in monkeys was relatively mild and compared with that commonly seen at the second or later serial passages of the virus in monkeys. Many of the test animals had been subjected to splenectomy immediately prior to inoculation, but among them were, unavoidably, a number of *Macacus maurus* monkeys which so far we have not proved to be a suitable laboratory animal. The *Macacus irus*, also used when our supply of *Macacus mulatta* monkeys ran out, belonged to a batch infected with malaria; animals not used for experiment appeared quite well, but after splenectomy the temperature became very irregular, large numbers of malarial parasites appeared in the blood, and several of the animals died.

Inoculation of Infective Material into the Amniotic Cavity.

Material from later cases (XXII to XXVI), causing no infection in monkeys, was inoculated into the amniotic sac of developing chicks by the new technique of Burnet.[34] No macroscopic or microscopic lesions resulted in the embryos, and subsequent passage to monkeys from which the spleen had been removed gave negative results after six to eight chick transfers.

Discussion.

Perhaps one of the chief conclusions to be drawn from this study is that, in spite of the adoption of modern techniques, measles is a disease highly refractory to experimental investigation. Towards the end of a major epidemic we were unable to isolate the virus in either monkeys or eggs. By inoculating monkeys with bacteria-free material from human cases at the height of the epidemic, we obtained in the majority of instances a reaction considered to be due to experimental measles; with bacteriologically sterile material the condition was passed from monkey to monkey for a limited number of passages. Of this reaction leucopenia was probably the most constant component; a rise of temperature was rather infrequent in later passages, rash and cough occurred irregularly in the earlier passages. It was unusual to observe all these signs in a single animal, and if the very severe criteria of infection adopted by Blake and Trask[1][2] were demanded, very few of our experiments (or those of other writers) could be considered to have given positive results. Other observers (for example, Plotz[3] and Anderson and Goldberger[4][5][6]), however, have found that a proportion of monkeys inoculated with material of proven infectivity show only some of the symptoms commonly associated with the disease in man.

Blake and Trask make the following statement:

> The evidence for a positive transmission has depended, as in the clinical diagnosis of measles, upon the development of the characteristic symptoms and lesions of the disease, the temperature and leucocyte counts having been recorded merely as additional data and not as evidence of a successful inoculation.

They inoculated intratracheally unfiltered or filtered nasal washings taken six or three days before the rash

TABLE IV.

Attempts to Grow the Virus of Measles on the Chorio-allantoic Membrane.

Source of Material Inoculated into Eggs.	Results of Inoculating Monkeys.	Number of Passages in Eggs.	Animal in which Last Egg-passage was Tested.	Result.
1. Defibrinated blood from Cases XVI, XVII and XVIII. 2. Filtered nasal washings from Cases XVI, XVII and XVIII.	Doubtful.	5 5	*Macacus mulatta.*	No temperature reaction. Leucocytes fell from 14,000 to 5,000 per cubic millimetre between ninth and twelfth days. No rash. Subsequent immunity test with known infectious material; no reaction.
3. Defibrinated blood from Cases XIX and XX.	Not tested.	5	*Macacus mulatta.*	No definite result.
4. Filtered nasal washings from Cases XIX and XX.	Not tested.	5		
5. Mixed 5th egg-cultures of 3 and 4.	—	14	*Macacus mulatta* (8).[1]	No definite result.
6. Defibrinated blood from Case XXI.	Positive.	12	*Macacus maurus* (8).	Nil.
7. Filtered nasal washings from Case XXI.		14	*Macacus irus* (8).	Malaria.
8. Mixed 12th and 14th egg-cultures of 5 and 6.	—	16	*Macacus mulatta* (8).	Nil.
9. Mixed blood taken at height of temperature reaction from three 1st-passage monkeys.	Positive.	7	*Macacus irus.*	Nil.
10. Blood of 3rd-passage monkey with pronounced leucopenia but no temperature.	Positive.	14	*Macacus mulatta* (8).	Temperature reaction eighth to eleventh day. Maximum rise 1° F. on ninth day. Leucocytes fell from 10,000 to 6,000 between ninth and fourteenth days. No rash.
11. Blood, liver, spleen and lymph gland of 4th-passage monkey.	Positive.	12	*Macacus maurus* (8).	Nil.
12. Blood, liver, spleen and lymph glands of 2nd-passage monkey.	Positive.	12	*Macacus irus* (8).	Malaria.
13. Blood, liver, spleen and lymph glands of 3rd-passage monkey.	Positive.	28	*Macacus mulatta* (8.)	Nil.
14. Blood, liver, spleen and lymph glands of 4th-passage monkey.	Positive.	24 28		

[1] 8 = Animal subjected to splenectomy immediately before inoculation.

or one or twenty-two hours after its appearance. After an incubation period varying from six to ten days their monkeys exhibited various symptoms, including listlessness and drowsiness, catarrhal conjunctivitis, enanthem and exanthem, and leucopenia. The disease was taken through six subsequent passages by intratracheal injection of suspensions of affected skin and buccal mucosa, or occasionally by intravenous injection of citrated blood, which was infective from the onset of the disease to at least the second day of exanthem.

The symptomatology in our monkeys differed considerably in detail from that recorded by Blake and Trask. Although frequently absent when the virus lost virulence in later passages, a febrile reaction was more constant in our primary passages than in those of the American authors. Conjunctivitis was not present in our animals; on the other hand, cough was a feature in many, while Blake and Trask commented on the entire absence of symptoms of rhinitis and bronchitis so characteristic of the disease in man. In this connexion it may be repeated that our monkeys rarely coughed while under direct observation, though often a burst of coughing preceded the entry or followed the departure of the observer from the room. We were never able to convince ourselves of the existence of an enanthem, and the distribution of the exanthem in our monkeys was different from that recorded by Blake and Trask; in their animals it affected most frequently the face, abdomen, arms, thighs and legs, while in ours it tended to become localized around the ischial tuberosities, on the perineum and on the thighs. The significance of diarrhœa occurring in the course of measles in the monkey is not wholly clear. It is well known that monkeys are frequent carriers of dysentery bacilli, and two of our animals died with dysenteric symptoms without developing measles; it seems possible, therefore, that diarrhœa in the course of measles may be due to activation of a latent dysentery.

Prior to the work of Blake and Trask, and following it, various writers have claimed successful transmission of measles to monkeys.

Among these, Anderson and Goldberger[4][5][6] found that mixed human buccal and nasal secretions were infective at the onset of the exanthem and again forty-eight hours later, while human blood was infective from just before the appearance of the rash until about twenty-four hours afterwards. Their monkeys developed fever, with or without respiratory symptoms such as sneezing and cough, and with or without an exanthem. The virus was filtrable, resisted desiccation for twenty-four hours over sulphuric acid in the cold-room, lost virulence in fifteen minutes at a temperature of 55° C., and withstood freezing for twenty-five hours. It was passed for as many as six passages without loss of virulence. The period of incubation was variable; it was not less than five days, and possibly extended to twenty-six days in one animal. Lucas and Prizer[7] confirmed these observations and noted the occurrence of enanthem and leucopenia in infected monkeys. Nevin and Bittman,[8][9] Otero and McKinley,[10] Degkwitz,[11] Purdy,[12] and Plotz[13][20] made similar observations.

With the exception of Anderson and Goldberger, who obtained positive results in *Macacus irus* (*cynomolgus*) and *Macacus radiata* (*sinicus*), these workers used exclusively the common rhesus monkey (*Macacus mulatta*). In view of the comments of Degkwitz[11] and Degkwitz and Mayer[12] regarding the suitability of this monkey as a laboratory animal—their claim of about 10% of successful inoculations appears much too conservative — we attempted to reproduce the disease in a number of species. As related, we were successful in primary passages with *Macacus mulatta*, *Macacus radiatus* and *Cebus fatuellus*, while our experiments with *Macacus irus*, *Macacus maurus* and *Cynopithecus niger* gave apparently negative results. Since infection was observed in species as remote as those of the old and new worlds, it seems possible that the negative or doubtful results with three old world species, including *Macacus irus*, found susceptible by Anderson and Goldberger, may have been due to previous infection of these animals. Anderson and Goldberger cited a case of transmission of the disease by contact from man to monkey (Chavigny[1]), and obtained evidence of similar transmission in monkeys. The experience of our laboratory assistant suggests strongly the contagious nature of the disease in monkeys.

Unlike Anderson and Goldberger and Blake and Trask, we were unable to transmit the virus serially in normal monkeys without loss of virulence. In a limited number of experiments, however, terminated unfortunately by shortage of monkeys, it seemed that by inoculating infective material immediately after splenectomy this difficulty might be overcome. On the other hand, previous irradiation of animals with X rays did not increase their susceptibility to measles.

A number of writers have claimed successful transmission of measles to rabbits.

Starting with human blood, Nevin and Bittman[8][9] infected rabbits in series, and after as many as five passages were able to reproduce the disease in monkeys. Infection of the rabbit was accompanied by exanthem and enanthem appearing at the third to the eighth day. The injection of blood from infections other than measles was without effect. Grund,[13] using naso-pharyngeal washings, found that many rabbits gave positive reactions. Enanthem was very inconstant; pyrexia and leucopenia also were unreliable signs of infection. Conjunctivitis and signs of inflammation of the upper respiratory tract were present in 70% of reacting animals, and a cutaneous eruption in 75%. With blood taken during the eruptive stage of human measles, or with filtered naso-pharyngeal secretions, Duval and d'Aunoy[14][15] produced in rabbits "a specific reaction analogous in all essential features" to that in man. After an incubation period of two to five days, 90% of the animals developed fever and leucopenia; many had coryza, conjunctival injection, exanthem and enanthem. With passage the virus increased in virulence, and a number of animals died. Scott and Simon[16][17][18] regarded a febrile reaction and leucopenia as characteristic of measles in the rabbit; they did not notice skin signs in unshaved animals, nor rightly did they consider "snuffles" a symptom of significance. They claim to have transmitted the disease to monkeys by inoculation of blood from affected rabbits. On the other hand, Purdy[19] obtained no results in rabbits with human blood and nasal secretions infective for two monkeys, and Degkwitz and Mayer[12] also failed to infect rabbits.

It is not easy to reconcile these conflicting findings. When after the virus has been passed a number of times in rabbits it has been found possible to produce with their blood typical measles in monkeys, it is not likely that a spontaneous disease has been activated in the rabbits and passed from one animal to another. Yet, in our experiments, no evidence was forthcoming of successful transmission of measles to rabbits, even when the injection of infective material followed immediately upon splenectomy. The blood of our rabbits was passed to others in series without any apparent signs of disease. Owing to a shortage of animals we did not attempt to infect monkeys with rabbit blood.

During the last few years several workers have attempted to grow the virus of measles in tissue-cultures or on the chorio-allantoic membrane.

Wenckebach and Kunert,[21] Degkwitz and Mayer,[12] Plotz,[20] and Rake and Shaffer[22][23] have described such experiments. The details and photographs published by the first-named authors did not exclude the development of non-specific lesions on the membranes as an explanation of their findings, while Degkwitz and Mayer content themselves with the bare statement that virus was cultivated on the egg. Plotz obtained infection in a monkey with material from the tenth passage (at three-day intervals) in tissue-cultures. Rake and Shaffer, in the most comprehensive and critical study yet undertaken, found that the virus could be propagated by serial passage on the chorio-allantois in the absence of regularly occurring macroscopic lesions; after more than 20 passages they were able successfully to inoculate rhesus monkeys

[1] We have not been able to consult the original reference.

with their cultures, and to initiate fresh cultures from monkeys infected with material either of human or of egg origin.

A primary purpose of our investigation was to determine whether or not the virus of measles could be grown on the chorio-allantois; our results were comparable with, if less uniformly successful than, those of Rake and Shaffer. In two instances, after five and 14 egg passages respectively, symptoms compatible with a diagnosis of measles were produced in monkeys, and as mentioned, the results of a number of other experiments may have been vitiated by the unavoidable use of a batch of refractory monkeys, or of those in which splenectomy prior to inoculation led to the activation of latent malaria. Like Rake and Shaffer, we were unable to correlate the presence of virus in the membranes with regularly recurring specific lesions. This being so, even if growth on the chorio-allantois can be achieved with some regularity, the observation is of little practical value, since success can be gauged only by injection into monkeys. Our main object in cultivating the virus in developing eggs was to obtain a simple and inexpensive means of studying the virus and of performing tests for immunity *et cetera*; in the absence of characteristic lesions on the chorio-allantois, the monkey remains the only (and rather unsatisfactory and expensive) laboratory animal. It is probable that during egg propagation the virus loses virulence, and that after a sufficient number of passages it could be used in time of epidemic to produce mild human infections giving protection against a more virulent virus.

Summary.

1. Inoculation, by a combination of routes, of defibrinated blood and filtered (bacteriologically sterile) nasal washings from cases of human measles led to symptoms of measles in *Macacus mulatta*, *Macacus radiatus* and *Cebus fatuellus*. Similar experiments with *Macacus irus*, *Macacus maurus* and *Cynopithecus niger* gave apparently negative results.

2. Virus was thus isolated only at the height of the epidemic. Months later, when the epidemic was nearly over, attempts to transmit the disease to monkeys were unsuccessful.

3. Passage of the virus intramuscularly with defibrinated blood of infected monkeys, or with suspensions of their spleens, livers and lymph glands, led always to loss of virulence. In a limited number of experiments it seemed that the virus might retain its virulence if injected into monkeys immediately after splenectomy. General irradiation of monkeys with X rays did not increase their susceptibility.

4. Defibrinated blood kept frozen at −10° C. retained its infectivity for ten but not for twenty-three days. Dried in the frozen state over phosphorus pentoxide and stored *in vacuo* over phosphorus pentoxide at −10° C., infected tissues were avirulent after 152 to 294 days.

5. The symptomatology of measles in the monkey is discussed briefly.

6. Inoculations into rabbits, with or without splenectomy, gave apparently negative results.

7. It is probable that the virus may be grown on the chorio-allantoic membrane of developing hens' eggs, but without the production of characteristic lesions which would render the method of use in further studies.

8. A case of probable laboratory infection from a monkey is recorded.

Acknowledgements.

We are grateful for the consistent cooperation of the staffs of the Adelaide Children's Hospital and the Metropolitan Infectious Diseases Hospital, Northfield, and for the willing help afforded by many general practitioners in Adelaide.

References.

(1) F. G. Blake and J. D. Trask: "Studies on Measles. I. Susceptibility of Monkeys to the Virus of Measles", *The Journal of Experimental Medicine*, Volume XXXIII, 1921, page 385.
(2) F. G. Blake and J. D. Trask: "Studies on Measles. II. Symptomatology and Pathology in Monkeys Experimentally Infected", *The Journal of Experimental Medicine*, Volume XXXIII, 1921, page 413.
(3) H. Plotz: "*La rougeole inapparente chez le singe (macacus rhesus)*", *Comptes rendus de la Société de biologie*, Volume CXXVIII, 1938, page 141.
(4) J. F. Anderson and J. Goldberger: "The Period of Infectivity of the Blood in Measles", *The Journal of the American Medical Association*, Volume LVII, 1911, page 113.
(5) J. Goldberger and J. F. Anderson: "An Experimental Demonstration of the Presence of the Virus of Measles in the Mixed Buccal and Nasal Secretions", *The Journal of the American Medical Association*, Volume LVII, 1911, page 476.
(6) J. Goldberger and J. F. Anderson: "The Nature of the Virus of Measles", *The Journal of the American Medical Association*, Volume LVII, 1911, page 971.
(7) W. P. Lucas and E. L. Prizer: "An Experimental Study of Measles in Monkeys", *The Journal of Medical Research*, Volume XXVI, 1912, page 181.
(8) M. Nevin and F. R. Bittman: "Experimental Measles in Rabbits and Monkeys", *The Journal of Infectious Diseases*, Volume XXIX, 1921, page 429.
(9) M. Nevin and F. R. Bittman: "Further Notes on Experimental Measles in Rabbits and Monkeys", *The Journal of Infectious Diseases*, Volume XXXII, 1923, page 33.
(10) P. M. Otero and E. B. McKinley: "Experimental Measles in Monkeys (Macacus Rhesus)", *Puerto Rico Journal of Public Health and Tropical Hygiene*, Volume V, 1929, page 36.
(11) R. Degkwitz: "The Etiology of Measles", *The Journal of Infectious Diseases*, Volume XLI, 1927, page 304.
(12) R. Degkwitz and J. B. Mayer: "*Zur Züchtung des Masernvirus*", *Deutsche medizinische Wochenschrift*, Volume LXIII, 1937, page 1796.
(13) M. Grund: "Susceptibility of Rabbits to the Virus of Measles", *The Journal of Infectious Diseases*, Volume XXX, 1922, page 86.
(14) C. W. Duval and R. d'Aunoy: "Studies upon Experimental Measles. II. The Enathematous, Exanthematous, Pyrexial and Leucocytic Syndrome Produced in the Rabbit by Intravenous Inoculation of Blood from Cases of Human Measles", *The Journal of Experimental Medicine*, Volume XXXVI, 1922, page 231.
(15) C. W. Duval and R. d'Aunoy: "Studies upon Experimental Measles. III. The Symptom-Complex in the Guinea-pig and Rabbit Following the Intratracheal and Intravenous Injection of Filtered Nasopharyngeal Secretions from Cases of Human Measles", *The Journal of Experimental Medicine*, Volume XXXVI, 1922, page 239.
(16) J. M. Scott and C. E. Simon: "Experimental Measles. I. The Thermic and Leucocytic Response of the Rabbit to Inoculation with the Virus of Measles, and their Value as Criteria of Infection", *The American Journal of Hygiene*, Volume IV, 1924, page 559.
(17) J. M. Scott and C. E. Simon: "Experimental Measles. II. On the Occurrence of Protective Bodies in the Blood of Rabbits Following Inoculation with Blood or Naso-Pharyngeal Secretion from Cases of Human Measles", *The American Journal of Hygiene*, Volume IV, 1924, page 725.
(18) J. M. Scott and C. E. Simon: "Experimental Measles. III. On the Fate of the Measles Virus in the Inoculated Rabbit and its Viability outside of the Body", *The American Journal of Hygiene*, Volume V, 1925, page 109.
(19) W. J. Purdy: "Rabbits and Experimental Measles: With Some Observations on Blood Counts and Rabbit Temperatures", *The British Journal of Experimental Pathology*, Volume VI, 1925, page 210.
(20) H. Plotz: "*Culture 'in vitro' du virus de la rougeole*", *Bulletin de l'Académie de médecine*, Volume CXIX, 1938, page 598.
(21) G. K. Wenckebach and H. Kunert: "*Die Züchtung des Masernvirus*", *Deutsche medizinische Wochenschrift*, Volume LXIII, 1937, page 1006.
(22) G. Rake and M. F. Shaffer: "Resistance of Measles Virus to Ether", *The Journal of Bacteriology*, Volume XXXIX, 1940, page 40.
(23) G. Rake and M. F. Shaffer: "Studies on Measles. I. The Use of the Chorio-allantois of the Developing Chick Embryo", *The Journal of Immunology*, Volume XXXVIII, 1940, page 177.
(24) F. M. Burnet: "Influenza Virus Infections of the Chick Embryo Lung", *The British Journal of Experimental Pathology*, Volume XXI, 1940, page 147.

Reviews.

PERIODICITY IN CANCER.

ON the fly-leaf of Dr. Douglas Webster's book on "The Periodicity and Cause of Cancer, Leukæmia and Allied Tumours"[1] is the following quotation from Bland-Sutton, written in 1906: "In many instances cancer seems to have a period of quiescence, and then to enter upon a period of rejuvenescence exactly like a chronic infective disease." This is the keynote of the work before us—spaced periods

[1] "The Periodicity and Cause of Cancer, Leukæmia and Allied Tumours, with Chapters on their Treatment", by J. H. D. Webster, M.D., F.R.C.P.E., F.F.R.; 1940. London: Baillière, Tindall and Cox. Crown 4to, pp. 193, with illustrations. Price: 12s. 6d. net.

of activity of malignant tissues with intervals of relative quiescence. The hypothesis, if it can be established as true, demands close attention and has far-reaching implications and practical importance. One implication is that the periodicity may be due to a life cycle in a parasite, a virus for instance, whose presence is responsible for the origin and also for the continuation and progress of the cancerous process. Certain phases of the life cycle, such as periods of multiplication, might be expected to cause greater changes or more rapid reactions in the host's infected cells, or might liberate substances more inimical to the resistance set up by the surrounding healthy tissues.

Webster considers that the data he has collected, dealing with cases of carcinoma, sarcoma, leuchæmia and Hodgkin's disease, show clearly that there are definite periods when the disease progresses, with intervening periods when increase is slow. He believes the most important or standard period of activity to be about every thirty-three weeks, a half-period of sixteen and a half weeks being recognizable in some cases and multiples of the full or the half-period in others. Recurrences only at multiples of the full period on the whole suggest a more favourable prognosis, whereas cases in which recurrences at half-periods succeed recurrences at full periods generally progress to a fatal issue, which is probably near at hand.

The periods, the author states, "can be recognized by dating, as far as is possible, the onsets of a primary's growth-acceleration phases, or the intervals between a primary's growth increase and the first sign of a secondary manifestation, or between the earliest successive signs of secondary or metastatic disease". He has satisfied himself that periodicity does occur, and gives many examples of cases, both personal and from published works, in support of his contention. We must, however, frankly admit that we do not feel convinced by the examples set forth.

As evidences of activity are given such symptoms as "discomfort in right side of throat" or "pricking sensations in throat with some swallowing difficulty", or such signs as a recurrent nodule or enlarged glands. It must be very difficult to decide on such data the exact dates required for the estimation of periodicity. The symptoms mentioned above may not necessarily be associated with an increase of activity and the nodule may have appeared and the glands may have been enlarging for perhaps several weeks before being observed by the patient. The author himself allows for a variation of *plus* or *minus* three weeks. The subject demands further investigation by other observers.

Dr. Webster has naturally inferred that, if this periodicity exists, it probably means that a living entity, such as a virus, is responsible. He has searched for evidence of such a virus and has found, not only in cases of carcinoma and sarcoma, but also in simple neoplasms, leuchæmia, Hodgkin's disease and *mycosis fungoides*, "elementary bodies" or inclusions that he considers indicate the presence of a virus. Active phases of the virus should be responsible for cell multiplication. He finds that mitoses are much more frequent during the active periods, and it is only during such times that elementary bodies are likely to be numerous and to be detected. During the quiescent periods their location may be represented by inclusion bodies.

One chapter is devoted to the application of the periodicity theory to diagnosis and prognosis. The author also discusses various therapeutic measures, in addition to surgery, X rays and radium, mostly based on the view that a virus is present. As appendices, are given tables of dates of the various periodic intervals and three pages on the periodicity and cause of influenza. The author has traced a grouping of patients in which either the primary disease or recurrences or metastases had followed a few weeks after influenzal attacks. In an envelope inside the back cover is a doubled card for clinical purposes entitled: "Neoplastic Periodicity: Webster's Table of Dates."

Dr. Webster's book should be studied closely by all those engaged in cancer problems. It is stimulating and full of interest. If he is correct in his views, then a distinct advance has been made in the study of cancer and allied conditions.

A TEXT-BOOK OF BACTERIOLOGY.

IN the preface to the third edition of his "Text-Book of Bacteriology"[1] Dr. Fairbrother explains that the word "Medical" has been omitted from the title because the book has proved useful to junior students of bacteriology in faculties other than medicine. While we appreciate the truth of this statement, it seems not improbable that it is among medical students and clinical bacteriologists that the book will continue to find its warmest admirers, for in the arrangement of his material it is obvious that the author has had the medical application of bacteriology constantly in mind, and it is difficult to imagine a more successful presentation of the subject from this point of view.

The book fills a long-felt want between the simpler introductions to bacteriology and the more detailed and voluminous systems of bacteriology. This latest edition has been brought up to date and includes additions to some sections, those dealing with viruses and the staphylococci in particular. The book can be strongly recommended to all interested in the study of bacteriology as applied to medicine, and may be regarded as one of the best text-books on the subject yet published.

[1] "A Text-Book of Bacteriology", by R. W. Fairbrother, D.Sc., M.D., M.R.C.P.; Third Edition; 1940. London: William Heinemann (Medical Books) Limited. Medium 8vo, pp. 461, with illustrations. Price: 17s 6d. net.

BIOLOGICAL ASPECTS OF INFECTIOUS DISEASE.

TODAY a growing number of intelligent laymen demand knowledge of the contributions of science to modern life. Medical science has, perhaps, been rather backward in recording its achievements, sacrifices and problems. "Biological Aspects of Infectious Disease",[1] by Dr. F. M. Burnet, an Australian well known for accurate observations on the minutiæ of infectious disease, shows at once the broad philosophical outlook from which his observations have been made and his recognition of the need for making medical science less of a mystery and more a section of contemporary biology. In the preface the author writes: "It is possible that the biological approach gives a better starting point for the professional study of human infectious disease than a purely medical one." This is a statement with which we are in entire agreement.

This very interesting book deals mainly with infectious diseases due to bacteria, protozoa and viruses, how they spread in, and how they are combated by, the animal organism. In a concluding chapter the author considers possible future struggles between man and these infective agents. Apart from its value to laymen as a simple exposition of the past and possible future of our knowledge of infectious diseases, the book is a highly desirable supplement to the current education of medical students and practitioners.

[1] "Biological Aspects of Infectious Disease", by F. M. Burnet, M.D.; 1940. Cambridge: The University Press; Melbourne: G. Jaboor. Demy 8vo, pp. 318, with illustrations. Price: 15s. net.

A HANDBOOK ON RADIOGRAPHY.

A COMPACT hand-book of radiography has been produced by Dr. J. A. Ross.[2] Instead, however, of confining the subject matter mainly to the fundamental principles of radiography and their specific application and modifications to the more routine standard examinations of the various parts of the body, the author essays the impossible task of covering the whole field of radiography—even to kymography, tomography, encephalography, angeiography, pelvimetry and uterosalpingography—in one hundred and twenty-two small pages.

The attempt is further vitiated by a confusing looseness of phraseology, that makes understanding of many parts of the text difficult even for an experienced radiologist, to say nothing of the radiographer and student for whom, it is stated, the book is mainly written. Even the term "antero-posterior", for example, as applied to the view with tube anterior and film posterior to the part examined, has its meaning reversed in respect to the knee (page 27) and the patella (page 28), but not elsewhere; whilst we are told in the former case that the "film is placed below the knee joint", meaning beneath or posterior to the joint.

More serious, perhaps, is the surprising omission of many of the special views and positions that may be regarded as standard in modern radiographic practice—for example, the dorso-distal oblique view for fracture of the scaphoid and the lateral view of the arm taken through the chest, to mention only two.

The book contains some useful rules and directions, but altogether can scarcely be regarded as having fulfilled its purpose or as forming an important contribution to the bibliography of radiology.

[2] "A Handbook of Radiography", by J. A. Ross, M.A., M.R.C.S., L.R.C.P., D.M.R.E.; 1940. London: H. K. Lewis and Company Limited. Demy 8vo, pp. 134, with 67 illustrations. Price: 7s. 6d. net.

The Medical Journal of Australia

SATURDAY, MARCH 15, 1941.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

THE MENTAL HOSPITALS OF NEW SOUTH WALES.

SOCIETY today prides itself on the progress it has made in the treatment of insane persons. From the appalling days of the lunatic asylum when "mentally afflicted" persons were treated little, if any, better than wild beasts, we have passed to an era when humanity and medical science demand that persons who are the subject of mental disease shall be placed in surroundings that will favour recovery. Medicine, thanks to the labours of pathologists and clinicians, has at its disposal methods of treatment that will generally alleviate a patient's symptoms and often effect a cure. Society has become more humane; it has also become more conscious of the rights of the individual and of its duty to those of its members who are unable to care for themselves. Society, moreover, recognizes mental alienation as a disease and not a stigma, and it is gradually, we hope, passing beyond the stage when it will be satisfied with the treatment of those who suffer from mental disease, but will expect something to be done about its prevention. In these circumstances mental hospitals are no longer mere asylums, places of refuge from the world of care and trouble and mental stress; they are institutions charged with the care of the mentally diseased and with their treatment; they are also centres for the study of mental disease that both treatment and prevention may be perfected. It is with these ideas in mind that we would bring to the notice of medical and possibly some lay readers the latest report by Dr. J. A. L. Wallace, Inspector-General of Mental Hospitals for New South Wales.

Two years have passed since the mental hospitals of New South Wales were discussed in these pages; previously the interval was four years. Our last discussion followed the appearance of a report by Dr. Wallace and on the previous occasion the basis of our remarks was a report by his predecessor in office, Dr. C. A. Hogg. On both occasions the chief complaint of the Inspector-General was that of inadequate and antiquated accommodation; in the present instance (Dr. Wallace's report is for the year ended June 30, 1940) the same deficiencies are emphasized. During the year under review the number of new admissions was 1,354, this number being 47 less than in the previous twelve months; the number of voluntary admissions was 1,077, a decrease of 26 from the previous year; the number of inebriates admitted was 98 or 30 less than in the previous year. At the same time the total number of resident patients at the end of the twelve months was 31 more than at the end of the previous year. Accommodation is provided for 9,790 patients, but the actual number in residence is 11,150; this means that there is overcrowding to the extent of 1,361 patients. This is the point that should be proclaimed again and again to the public. This overcrowding is no new phenomenon. Dr. Wallace has drawn up a table covering this matter for the last twenty years. In the year 1938-1939, the year before the one under review, the number of patients in excess of the accommodation was 1,484; this was the peak figure for the last twenty years. In the year 1933-1934 the number was 657; this is the only year in which the number was less than 1,000 until we go back to the year 1922-1923, when it was 750. The decrease in the overcrowding as between the year 1939-1940 and the year 1938-1939 is accounted for by the fact that 119 new beds were provided and that 36 more were obtained by remodelling. (The increase in the number of patients, be it remembered, was 31.) In our discussion on this subject two years ago Dr. Wallace's complaints were championed in no half-hearted way and since then some of the deficiencies have been made good. Two years ago Dr. Wallace complained in the strongest possible words about the accommodation for female patients at Gladesville Hospital. He now writes that two new female refractory wards have been completed and he refers with satisfaction to "the mental improvement already shown by these women in their new surroundings and how destructive tendencies and excitement appear to be inhibited with the change to better and brighter environment". The improvement that has taken place at Gladesville will also occur at Parramatta if some notice is taken of Dr. Wallace's oft-repeated plea for fresh accommodation for the chronic refractory women patients. He states that the treatment of these patients is hampered by the structural difficulties of the buildings; two years ago he pointed out also that these buildings are of weatherboard and that in the event of fire the safety of the patients will be greatly imperilled. A start has been made at Kenmore to substitute new workshop buildings for the weatherboard structures that were a danger to the old men in the neighbouring weatherboard wards. At Stockton, new nursery wards to accommodate 200 mentally defective girls are under construction; this is good news, but it is somewhat offset by the fact that the present nurses' quarters are quite unfitted as residences for the nursing staff.

From the foregoing it will be seen that some, but only some, of the most glaring deficiencies on the structural side have been made good. The trouble is that the overcrowding still remains. The female wards at Parramatta and the nursing quarters at Stockton require immediate attention, and when what is necessary has been done in these places, steps should be taken to adopt Dr. Wallace's recommendation for the provision of new accommodation

near the metropolis. There must be no tinkering with this problem; it is urgent and imperative. To attempt the treatment of patients afflicted with mental disease in unsuitable or overcrowded surroundings is to revert to the unsavoury days of the asylum, and when these deplorable conditions are avoidable, comes perilously near to a denial of the institutions under discussion as hospitals. But it may be argued that in war time economy should be practised and that mental hospitals with all other State medical activities should be content with much smaller government allowances. The answer to this is twofold. In the first place the mental hospitals in New South Wales have been so starved of funds for many years that they have a great deal of leeway to make up before they can be regarded as adequately equipped to fulfill their function. In the second place, if economies have to be practised, they should be applied last of all to persons who suffer from mental disease, for they of all persons in the community are the most helpless; they cannot speak in their own behalf, and if they could they would have to overcome the idea still lingering in the minds of the unintelligent that the mentally diseased really are of no account, are both insensitive and insensible and are therefore not worth the time and trouble and money that certain well-meaning persons wish to spend on them. And mention of the war brings us to the final point and one that may possibly appeal to the laity, the politicians, who control mental hospitals. Dr. Wallace points out that the Psychiatric Clinic at Broughton Hall is already overcrowded and working under great disabilities. He foresees that the end of the war will in all probability bring to the doors of this clinic many persons suffering from psychoneurosis who should be admitted. He is to be congratulated on his foresight, and it is to be hoped that he will continue to urge on his Minister the immediate addition of buildings and equipment to this extremely valuable arm of the service.

Current Comment.

PLASMA PROTHROMBIN AND VITAMIN K.

THE discovery of any new and important therapeutic measure tends to be followed by the wide and uncritical use of the remedy concerned in any condition that remotely resembles the one in which it is specifically indicated. This has happened with vitamin *K*, which has proved of value in the hæmorrhagic tendency associated with obstructive jaundice. We therefore welcome a long, thorough and authoritative review of the literature on this subject by K. M. Brinkhous,[1] one of the workers who has been prominent in investigating the nature and activity of the new vitamin. It has long been known that prothrombin is an important factor in blood clotting. In the presence of calcium and thromboplastin it becomes thrombin, which then combines with fibrinogen to form the fibrin clot. Prothrombin is a heat-labile substance associated with the pseudo-globulin fraction of the plasma proteins. In human plasma stored at room temperature it slowly becomes inactive. If kept at 2° to 5° C. approximately 60% of it is still active at the end of three weeks. In stored blood, unfortunately, the rate of destruction is considerably more rapid, a fact to be remembered when blood from a blood bank is used for transfusions intended to raise the level of the plasma prothrombin. The liver is essential for the maintenance of a normal plasma prothrombin, for in poisoning, injury or removal of the liver the level in the blood falls.

Between 1928 and 1933 it was noticed by a number of separate workers that chickens fed with deficient diets for various reasons developed a hæmorrhagic tendency. This was associated with a low plasma prothrombin level and was traced to the absence from the chick's diet of a fat-soluble substance which is normally present in many foods and to which the name of vitamin *K* was given. It is not identical with prothrombin. Certain bacteria can synthesize the vitamin in foods from which it has been extracted by ether, and this happens in the bowel, even when a vitamin-free diet is fed. In such circumstances the vitamin is found in the fæces. The vitamin is fat-soluble, inactivated by sunlight or artificial light, by alkalis, oxidizing agents and strong acids. Unlike prothrombin, it is heat stable. It was early prepared as an oily substance and later as colourless crystals from alfalfa or fish meal. Chemically it is a naphthaquinone. Similar but not identical naphthoquinones have been synthesized and possess in marked degree the biological properties of the natural vitamin. This is found naturally in alfalfa, spinach, cabbage, cauliflower, kale, carrot tops, soya bean, nettle, chestnut leaves, pine needles and seaweed. Tomatoes, orange peel and hemp seed have been shown to be less rich. In general, green leaves are rich in the vitamin; leaves grown in the dark, and roots, fruits, nuts and seed are poor. A number of bacteria contain the substance in large amounts. *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Sarcinia lutea* and *Mycobacterium tuberculosis* are potently supplied. Human fæces contain a lot of the vitamin, partly because it is formed by bacterial action in the bowel. The urine, however, contains none. Various body tissues contain it. This supply is entirely exogenous and no tissue is a rich storehouse. The vitamin is absorbed from the bowel only in the presence of bile salts, for it is fat-soluble. If there is deficient intake or absorption of this vitamin, the level of prothrombin in the blood falls. There seems to be no doubt that vitamin *K* is a precursor of prothrombin.

The plasma prothrombin level falls in certain diseases because of liver damage. Cirrhosis is an example. This fall seems to be independent of the intake or absorption of vitamin *K*, and is unaffected by the ingestion of large amounts of the vitamin. Indeed the level of plasma prothrombin, if a vitamin *K* dietary deficiency can be excluded, is a useful index of liver function. In obstructive jaundice the hæmorrhagic tendency is due to a low level of plasma prothrombin, which in turn is due to a deficient absorption of vitamin *K* from the bowel because of the absence of bile salts. In most cases the tendency can be cured by the ingestion of bile salts and vitamin *K*. In the patients who do not respond to this therapy the jaundice is accompanied by a considerable degree of liver damage. The bleeding in obstructive jaundice is most severe during the few days after operation. During this period the plasma prothrombin level falls lower than it was before operation. The reasons suggested for this are the large call on prothrombin for clotting of blood during operation, the damage to the liver by operative trauma and by anæsthesia, and the occasional drainage of bile to the exterior by a tube. By way of therapy, vitamin *K*, either synthetic or natural, should be given with bile salts for several days before operation. Preparations of the vitamin can be given by hypodermic or by intramuscular injection, but absorption is very much slower and less effective than if the oral route is used. The response to intravenous injection is rapid and marked, and this seems to be the ideal route for patients who vomit. Bile salts, of course, need not accompany parenteral administration.

Hæmorrhagic disease of the new-born is another condition in which a bleeding tendency is associated with and seems to depend on a deficient plasma prothrombin content, a relationship that was discussed in this journal on September 7, 1940. The low level of this constituent of the blood of infants can be remedied by the administration of vitamin *K*. Only in a few cases has hæmorrhagic disease of the new-born been treated in this way; but results have been encouraging. The number of cases is still too

[1] *Medicine*, September, 1940.

small for the results to be considered conclusive, and transfusion of adult blood remains the safest and most effective way of treating this disease. It too effects a considerable rise in the very low level of prothrombin in the blood of the new-born. The plasma prothrombin has been investigated in a number of other diseases. In certain abnormal conditions of the intestines, such as ulcerative colitis and sprue, a deficiency of this substance has been found in a few instances, presumably because of impaired absorption from the bowel. In none, however, has it been of sufficient degree to produce a tendency to hæmorrhage. In artificially induced fever a fall in both blood platelets and prothrombin has been found. It is suggested that this is due to damage to the liver, probably temporary in nature. In *icterus gravis neonatorum*, hæmolytic anæmia of the new-born and *hydrops fœtalis* a similar prothrombin deficiency has been found, but it is probably only the physiological deficiency of the neonatal period and not a direct cause of the disease process. This group of diseases is not characterized by a pronounced tendency to hæmorrhage. In hæmophilia, on the other hand, there is a very pronounced hæmorrhagic tendency, but no deficiency of prothrombin. The bleeding is due to a delay in conversion of prothrombin to thrombin. There are a number of reports of examples in which vitamin *K* has been tried as a therapeutic measure in hæmophilia, but in none has any significant improvement been effected. In leuchæmia, thrombocytopenic purpura and aplastic anæmia hæmorrhage also occurs with undue frequency and ease, but again the reason is not a prothrombin deficiency and vitamin *K* is of no use in treatment.

The present state of our knowledge therefore indicates that this new vitamin is of value in the treatment of the hæmorrhagic tendency of only obstructive jaundice and hæmorrhagic disease of the new-born. In addition it is unquestionably an important constituent of any normal diet, but since it is widespread in green leaves and vegetables and is heat stable it seems unlikely that many people will fail to obtain an adequate supply in their common diet. How much further its field of importance and usefulness will be found to extend, only time can tell.

PULMONARY HYPERTENSION.

THE clinical curiosity of yesteryear, multiplied from time to time by fresh reports, which are at length collated and reviewed, is the "new disease" of today. Of recent years some twenty instances have been reported in ones and twos in the literature of the occurrence of a cardiological curiosity characterized by considerable hypertrophy and ultimate failure of the right ventricle of the heart, and by pulmonary vascular atherosclerosis in the absence of pulmonary disease or any of the factors commonly supposed to cause congestion in the pulmonary vascular bed. These reports were collected in 1935 by D. Brenner, under the heading of "primary pulmonary arteriosclerosis". At a meeting of the Cardiac Society of Great Britain and Ireland in 1939, a number of cases of this curiosity were presented, the condition was discussed, and from reports recently published it is clear that ideas as to its essential nature have become clarified to the point at which it may be said that a new disease has been described. S. de Navasquez, J. R. Forbes and H. E. Holling report three cases of this disease.[1] In each instance the patient died, and the great enlargement of the right ventricle was confirmed by autopsy and measured by dissection of the heart and weighing of the ventricles separately; in each case the left ventricle weighed less than the right, instead of about three-quarters as much again as the right as normally. The generally recognized causes of such hypertrophy due to disease of the heart and lungs were found to be absent. The authors give a detailed description of the clinical and pathological features which were present. They confess themselves at a loss to suggest the pathogenesis of the disease, and they suggest that it should be known by the name of "idiopathic right ventricular hypertrophy", rejecting the terms "pulmonary arteriosclerosis" and "pulmonary hypertension", since the vascular changes bear no relationship to the degree of ventricular hypertrophy. Also they found no evidence of the changes seen in the small arteries and arterioles of the systemic circulation when systemic hypertension is present, although, as they point out, the small muscular arterioles which are chiefly affected in systemic hypertension are absent in the lung. "Does this single anatomical fact [of great hypertrophy of the right ventricle] justify the opinion that the hypertrophy is a physiological reaction to increased work?" ask the authors. Doubt as they will, Wolff's law is seldom fallacious, and it seems likely that the name "pulmonary hypertension" will stick until an ultimate cause is discovered. In the clinical nomenclature of systemic high blood pressure dubiety as to the ultimate cause has long since led to a flight from morbid anatomical associations.

T. East[1] also reports three fatal cases of the disease and gives a very clear description of the clinical picture, which he states should be fairly easily recognizable during life. He summarizes the clinical features as follows: enlargement of the right ventricle with the characteristic electrocardiogram; enlargement of the pulmonary artery, confirmed by X-ray examination, and a loud pulmonary second sound "suggesting a high pressure in it"; progressive and intractable failure of the right ventricle, with the maintenance of normal rhythm, dyspnœa of any severity being absent; a normal radiographic appearance of the left auricle; an absence of valvular or septal defects; an absence of pulmonary disease and an absence of evidence of syphilis. East mentions that the absence of dyspnœa in his patients was very striking; the veins filled up, the liver became engorged and the cyanosis increased, but the pulmonary circulation was unimpeded, so that the breathing continued to be easy until the patient was nearly dead. The picture was one of a pure and rapidly progressive failure of the right ventricle, bearing out fully the modern theory that cardiac dyspnœa is the result of engorgement of the pulmonary circulation.

Interest in this curious and hitherto rarely recorded condition will undoubtedly be stimulated by the publication of the reports referred to, and as further cases come to light we may expect to hear further discussion on the nomenclature and on the morbid histology of the pulmonary arteries—to what extent their abnormal state is due to intrinsic causes and how much to excessive wear and tear due to the disease.

[1] *British Heart Journal*, July, 1940.

"HIGHWAYS TO HEALTH."

IN April of last year reference was made in the editorial columns of this journal to the formation by the New South Wales Branch of the British Medical Association of a Department of Medical Sociology and Research. The object of this department was the rendering of "a public service by collecting information and compiling records of medical and sociological importance based on accurate information for dissemination among the public by every available channel, such as the public Press, public addresses and broadcasting". In the latter half of 1940 the new department made its bow to the public in a series of talks entitled "Highways to Health", broadcast over the national network of the Australian Broadcasting Commission. The talks aroused great interest and soon a large "fan mail" was received. A reply was sent to every letter, and some of the letters came from people who were seeking information on questions raised in the talks. Twelve of these talks by the "B.M.A. Spokesman" have been published in a small brochure that can be bought for the modest sum of one shilling.[2] Members of the several Branches are asked to bear this publication in mind and when opportunity offers to recommend it to their patients and their friends.

[1] *British Heart Journal*, July, 1940.

[2] "Highways to Health", talks by the B.M.A. Spokesman; 1941. Sydney: Angus and Robertson Limited. Crown 8vo, pp. 88. Price: 1s. net.

Abstracts from Medical Literature.

SURGERY.

Carcinoma of the Lung.

J. J. SINGER (*Surgery*, December, 1940) contributes a clinical study of primary bronchogenic carcinoma. The age incidence is approximately the same as in other cancers; but a case has been reported by Schwyter in an infant, aged sixteen months. Males predominate in the ratio of about three or four to one. Two-thirds of the growths occur in the right lung. Dry irritating cough is an early symptom. Pain out of proportion to the physical signs seems to be suggestive. Dyspnœa may be complained of if sudden atelectasis occurs; but in slow contraction of the lung little breathlessness is found. Loss of weight, fever and Horner's syndrome are late symptoms of the complications. X-ray examination shows appearances due not only to the tumour, but to its consequences, such as atelectasis, bronchiectasis, pneumonia, abscess, emphysema, pleural effusion *et cetera*. Bronchography by use of iodized oil may show irregularity or closure of a bronchus and deformed distribution of the bronchial tree. Clinical suspicion of carcinoma can only be confirmed by demonstration of the cancer cells. Direct vision by bronchoscopy of growths in the larger bronchi enables biopsy specimens to be obtained. In other cases thoracoscopy can be performed and pleural or lung biopsy material obtained. Pleural fluid may be aspirated and examined microscopically. Finally thoracotomy may be necessary before diagnosis can be confirmed. Even after all these investigations an occasional case will defy diagnosis except by autopsy. Two cases are reported which illustrate some of the diagnostic difficulties.

Surgery and the Abdominal Aorta.

DANIEL C. ELKIN (*Annals of Surgery*, November, 1940) gives an account of the operation of ligature of the abdominal aorta for aneurysm and reports a case. It appears that 24 cases have previously been reported since the first one by Sir Astley Cooper in 1817. Most of the patients have been suffering from aneurysms of the iliac or femoral arteries or from gunshot wounds, but ten had aortic aneurysms. Most of the patients died soon after the operation, from hæmorrhage, sepsis or shock; but it must be noted that four cases were in the pre-anæsthetic era and nine in pre-Listerian times. In the past twenty years, however, the six patients whose records have been reported, have all survived operation and lived with relief of symptoms for varying periods. Some of them died of quite unrelated conditions; for instance, in one case hæmoptysis from pulmonary tuberculosis, and in another intestinal obstruction. The author's own case was one of aneurysm of the lower end of the abdominal aorta, involving the commencement of each common iliac artery. Six months before, the patient, a man, aged sixty-one years, had noticed a swelling in the left side of the abdomen, which gradually increased in size, caused pain, at first intermittent, but later constant, and cramps in the legs. A month before admission he had noted pulsation in the swelling. Proximal ligature with two pieces of quarter-inch cotton tape was performed; but the lumen was not completely occluded, as collateral circulation was not good. The patient returned home two weeks later, at which time the aneurysm could be felt, much smaller than before, as an indurated mass in the left lower quadrant of the abdomen, without pulsation or bruit. Four weeks after operation the patient resumed his work as a country minister. He was still working actively eleven months later.

Peritoneal Adhesions.

EDWIN P. LEHMAN AND FLOYD BOYS (*Annals of Surgery*, November, 1940) make a progress report on their experiments with heparin in the prevention of abdominal adhesions. They commenced this work on the theory that heparin, if introduced into the peritoneal cavity after operations, should prevent the formation of fibrin, which is an essential preliminary to the formation of fibrous adhesions. A previous report had revealed that after the introduction of heparin into the abdomen of the laboratory animal, many fewer adhesions formed or reformed than when no such solution was used or when fluids such as normal saline solution or amniotic fluid were introduced. Some doubt was expressed in the preliminary report whether heparin might lead to internal hæmorrhages in the abdomen. This point has been settled by further experiment, and the authors conclude that, provided efficient hæmostasis is secured at operation, there need be no fear of this complication. A further series of experiments gives some indication that there is an optimum dosage to be used and that the substance should be introduced not only at operation but also on two subsequent days. It was thought that the introduction of heparin at the time of the original production of the adhesions (which was performed by perforating the tip of the appendix and smearing a measured amount of its expressed contents over the lower part of the ileum and the caecum, and also by scarifying the peritoneum with dry gauze) might lead to a higher immediate death rate from general peritonitis, as the presumed localizing effect of fibrinous exudate and formation of adhesions might be removed. The authors' experiments on this point show that the death rate from immediate general peritonitis was not significantly raised.

Ischæmic Contracture in the Lower Limb.

THOMAS HORWITZ (*Archives of Surgery*, October, 1940) reports two cases of a condition of the lower limb identical with Volkmann's contracture of the upper limb. He also reviews eighteen previously reported cases. The condition occurs as in Volkmann's ischæmic contracture where there has been injury to the soft tissues or bones of the limb followed by considerable swelling inside the fascial compartments, leading to obstruction to the venous return from the limb. In each of the author's cases the condition followed a fracture of the shaft of the femur. In the acute stage the symptoms are acute pain, cyanosis, œdema, paræsthesia, hyperæsthesia, loss of motor power and trophic changes. This condition passes into a stage of induration and rigidity of the muscles, associated with fibrosis and contraction, with areas of necrosis and calcification. Deformity usually occurs in the nature of a *talipes equinovarus* with restriction or complete loss of movement at the ankle joint and the joints of the foot. Hammer-toes occur. Vascular pulsations are sometimes but not always diminished. Intractable pain sometimes occurs. Prophylaxis consists of incision of the deep fascia at an early stage of the acute process. In the established late stage deformities may require operative correction.

Acute Perforation in Gastric Carcinoma.

MELVIN A. CASBERG (*Archives of Surgery*, October, 1940) reviews the records of 247 patients with gastric carcinoma admitted to the St. Louis City Hospital in a ten-year period, in which seven cases of acute perforation of the lesion occurred, and reports two more recent cases. The average age over the whole series was sixty-three years, whereas the average age in the cases of perforation was fifty-one years. The perforations all occurred in males. The difficulty of pre-operative diagnosis of a perforated carcinoma may be great, as abdominal rigidity obscures the signs. The history alone may be of assistance. The treatment consists in laparotomy after attention to shock has received adequate consideration. Simple suture is recommended, more extensive procedures being left till a later date if the patient survives the emergency. The death rate seems higher than in perforation of simple ulcers. Suture of the perforation may be difficult because of the friability and induration of the tissue. Closure with omentum is usually necessary. Drainage is always used because of this difficulty in securely closing the defect. It is recommended that biopsy specimens should be taken from all patients who have suffered a perforation of the stomach from gastric ulceration.

Cancer of the Tongue.

HAYES E. MARTIN, HILMAR MUNSTER AND EVERETT D. SUGARBAKER (*Archives of Surgery*, October, 1940), in a discussion on cancer of the tongue, give a review of 556 patients admitted during eight years to the Memorial Hospital for Cancer and Allied Diseases. The average age of the patients was fifty-eight years. Males were in the proportion of 87%, and females 13%. The authors state that one-third of the growths occur on the posterior third of the tongue, more than half on the lateral aspect of the middle third, the remainder being on the anterior third. Cancer practically never occurs on the dorsum of the middle third. Chronic irritation appears to be a causative factor. Leucoplakia occurs very frequently as an antecedent. One-third of the patients reacted to the Wassermann test. Usually in the early stages pain is absent. In most cases in the authors' series the patient presented himself because he felt or saw the swelling rather than because of pain or other symptoms. In growths of the posterior third, which the patient does not feel or see, the first complaint was most frequently the presence of metastatic glands in the neck. There is great variation in the type of growth from the deeply infiltrating but slightly ulcerating growth to the type in which there is fungation with, perhaps, little infiltration. Among other varieties is the slightly indurated fissure in a patch of leucoplakia. In the diagnosis

the authors insist on the importance of performing biopsy at the first examination and, if necessary, repeating this procedure. The relative frequency of cancer, tuberculous ulcer and gummatous ulcer of the tongue is about 100 : 3 : less than 1. Tuberculous ulcers are usually painful, with little induration, and are almost always secondary to demonstrable pulmonary tuberculosis. A gummatous ulcer should heal under aggressive anti-luetic treatment in three or four weeks. Early in its course cancer of the tongue invades other structures, such as the floor of the mouth, tonsillar pillars or base of the tongue. Few cases are found which are suitable for operative treatment alone. A full account is given of the technique of treatment by operation, Röntgen irradiation and radon seed implantation, with the indications for each in various cases. The authors mention that the staff at the Memorial Hospital consists of surgeons trained in all three methods, so that an unbiased judgement is obtained on the therapeutic method or combination of methods to be used.

Treatment of Post-Operative Atelectasis.

JOHN A. GIUS (*Surgery*, November, 1940) points out that hypoventilation occurs after all abdominal operations, especially those on the upper abdominal organs. The cause is reflex spasm of the abdominal muscles and the diaphragm due to pain from the wound. This leads to inability to cough effectively, the retention of secretions, and bronchial blockage. The air in the distal alveoli is absorbed, and collapse of portion of the lung occurs. Infection from the upper part of the respiratory tract may commence and pneumonia then supervene. It has been shown that anæsthesia of the abdominal wound can increase the vital capacity, which is usually 20% to 40% after abdominal operations, to 90% of the normal. The usual methods of obtaining the removal of the plugs of mucus are active breathing and coughing, which are difficult, carbon dioxide inhalations, changes of posture, vigorous percussion over the collapsed lobe, the administration of expectorants, and bronchoscopic removal. The common practice of administering morphine after operations accentuates hypoventilation and still further depresses the cough reflex. The author has used and recommends anæsthesia of the wound area by paravertebral "Procaine" block. This allows free active coughing and assists removal of the plug. In three cases in which this method of treatment was used, satisfactory and quick resolution of the atelectasis was obtained. Support of the abdominal wall is recommended to prevent separation of the anæsthetic abdominal wound.

Vitamin K in Hepatic Disease.

J. G. ALLEN AND O. C. JULIAN (*Archives of Surgery*, December, 1940) present data concerning the response of plasma prothrombin to vitamin *K* therapy in patients with hepatic disease. The patients, 12 in number, had various forms of liver disease, including acute hepatitis, alcoholic cirrhosis, secondary carcinoma of the liver (without icterus) and acute yellow atrophy. They received daily by mouth 8·0 milligrammes of 2-methyl-1, 4-naphthoquinone, accompanied by bile salts. In ten cases there was no response and in the other two a delayed rise in prothrombin level. This is strikingly different from the response in patients with hypoprothrombinæmia due to obstructive jaundice. The authors believe that prothrombin response is a characteristic of diagnostic significance. The above and other evidence indicate that the liver is the site of prothrombin formation, and lack of response to adequate vitamin *K* therapy would imply intrahepatic disease, rather than obstruction of bile ducts, as the cause of jaundice.

Parenteral Administration of a Compound with Vitamin K Activity.

E. R. ANDERSON, J. E. KARABIN, H. UDESKY AND L. SEED (*Archives of Surgery*, November, 1940) discuss the parenteral administration of water-soluble compounds with vitamin *K* activity. Vitamin *K* itself is oil-soluble and is inconvenient for parenteral use. Oral administration has several disadvantages. Patients who are vomiting cannot retain the vitamin, while in other cases some intestinal disorder may interfere with or prevent absorption. By intravenous or intramuscular injection a rapid and satisfactory response is encountered, unless liver function is in abeyance; thus in the only unsuccessful case reported, the liver was found to have been destroyed almost totally by acute yellow atrophy. The compound used by the authors was 4-amino-2-methyl-1-naphthol hydrochloride, which is water-soluble and which they designate as vitamin K_5. This compound was given by intravenous and intramuscular routes to 18 patients with hypoprothrombinæmia. Prothrombin determinations by the Smith method were made and the results graphed. With one exception the response to intravenous injection of vitamin K_5 was rapid and striking. The rise in prothrombin content was definite after one hour, while normal prothrombin level was reached after from two to twelve hours, depending on liver function. The average dose was 2·0 to 3·0 milligrammes daily. The intravenous route was found to be superior to the intramuscular. No toxic effects were observed from doses of up to 6·0 milligrammes. The oral administration of bile salts is not necessary when vitamin K_5 is given parenterally.

Amputation of the Leg in Diabetic Gangrene.

SAUL S. SAMUELS (*Annals of Surgery*, July, 1940) discusses the indications for and precautions in amputation of the leg for diabetic gangrene, describes a method of amputation and reviews his personal experiences. The two major indications for amputation are rapid spread of gangrene without demarcation and the presence of uncontrollable infection in the foot. Pre-operative treatment must be simplified; transfusions and intravenous injections of glucose and saline solution with insulin are not needed unless there is dehydration. If the patient's urine cannot be made sugar-free before operation by large doses of insulin, it is an indication that undrained infection is present in the foot. The author stresses the need for careful choice of an anæsthetic agent. He prefers "Cyclopropane". Ether and spinal anæsthesia are considered unnecessary and possibly dangerous. The author recalls the previous teaching that in infected diabetic gangrene the infection would spread into the thigh or even throughout the body if adequate precautions were not taken, so that it was advised that these should include leaving the stump wide open, inserting drains into a partly sutured stump, or leaving untied sutures to be tied later if the wound remained clean. The delayed healing consequent upon the observance of these precautions contributed largely to the high mortality, in some hospitals as high as 75%, as these patients required a prolonged stay in bed and often developed bed-sores, pneumonia *et cetera*. The author considers that undue stress has been laid on the dangers of post-operative wound infection, and has devised a simple amputation with immediate suture of the wound. He reports that of 33 patients whose limbs he had amputated, only three died, a mortality rate of 9%, and that most of his patients were discharged from hospital on the seventh to the tenth day with instructions to get about on crutches. The level of amputation is supracondylar, to leave a long stump for the fitting of an artificial leg. No tourniquet is used. A simple circular incision without flaps is employed and is made at the upper border of the patella. The sciatic nerve is not injected with alcohol or "Novocain" and is merely cut cleanly through with a sharp knife. The femur is divided about two inches proximal to the skin incision. Plain catgut was at first used for ligatures and buried sutures, but in the later cases was replaced by silk, with very gratifying results. The patient may be allowed out of bed on the day after operation and thereafter be permitted to sit in a wheel-chair. Reduction in the dosage of insulin is usually necessary once the septic focus has been removed.

A New Suture Material.

J. E. BELLAS (*Archives of Surgery*, December, 1940) presents the results of a study of various sutures and describes the features of a new suture material. Discussing the controversy on the merits of absorbable and unabsorbable sutures, which has raged for so many years, he suggests that instead of this classification, emphasis should be placed on whether a certain suture is reacting or non-reacting; that is, whether or not it stimulates a reaction in the tissues in which it is buried. After extensive experimental and clinical trial he has produced a suture which he has named "plastigut", based on the principle of non-reaction. This suture is of synthetic plastic composition. The author states that it is also non-capillary and non-absorbable.

Bleeding Œsophageal Varices.

WALTMAN WALTERS, H. J. MOERSCH AND D. A. MCKINNON (*Archives of Surgery*, November, 1940) review the ætiology and management of œsophageal varices and describe a method of treatment by the injection of a sclerosing solution by means of a needle inserted under direct vision through an œsophagoscope. The method was employed in six cases, with satisfactory results in four. Some of these patients had previously been treated by other methods, such as splenectomy. The authors, who approached with some diffidence the use of the œsophagoscope in the presence of œsophageal varices, did not find that passage of the instrument caused any bleeding. They conclude that the method is worthy of further trial.

British Medical Association News.

SCIENTIFIC.

A meeting of the New South Wales Branch of the British Medical Association was held on September 26, 1940, at the Robert H. Todd Assembly Hall, British Medical Association House, 135, Macquarie Street, Sydney, Professor W. K. Inglis, the President, in the chair.

Symposium on Diabetes.

The meeting took the form of a symposium on diabetes.

Hypoglycæmia.

Dr. F. Hales Wilson spoke on hypoglycæmia. He said that hypoglycæmia or lowering of the blood glucose level below the normal lower limit of about 80 milligrammes per 100 cubic centimetres might be due to a variety of causes. Joslin had mentioned as the chief causes: (i) prolonged undernutrition, (ii) prolonged exercise, (iii) overdosage of insulin, (iv) Addison's disease, (v) hypothyreoidism, (vi) hypopituitarism, (vii) destructive liver disease, (viii) islet cell tumour and (ix) increased sensitivity to insulin in the terminal stages of pulmonary tuberculosis. In the treatment of diabetes, insulin overdosage was naturally the chief cause of hypoglycæmia; but one should bear in mind the possibility of other causes, such as hepatic cirrhosis.

Dr. Wilson went on to say that the typical symptoms were well known and consisted of hunger, weakness, mental confusion, blurred or double vision *et cetera*; but different individuals varied greatly in their manifestations of hypoglycæmia, and it was a wise rule that any unusual behaviour or symptom in a diabetic using insulin should be considered due to hypoglycæmia until this was disproved, and especially if the condition recurred at the same time on other days. From mere shortage of glucose in the blood, the hen-pecked, pious and docile husband might become a storming dictator, whose better half recoiled aghast at the vehemence of his language. A returned soldier, who in 1919 used to awaken in the small hours in a state of acute anxiety and agitation, recently developed diabetes; when he was treated with insulin his "nerve attacks" returned, but they readily abated with an increase of carbohydrate for supper. A housewife had reported that she felt extremely well except for great lassitude when preparing the evening meal; a little carbohydrate with afternoon tea soon restored her energy.

Diagnosis was made by consideration of symptoms and signs; sweating was usually present, and if minimal it was best detected by placing the palm of the hand on the forehead, where the skin would be found to be clammy. The pulse was usually rapid, but in very severe cases bradycardia might be present. It should be remembered that urine obtained at the time might have been secreted by the kidney when the blood sugar level was above normal, and might therefore contain sugar. In doubtful cases appeal should be made to blood sugar estimation.

The occurrence of hypoglycæmia indicated a lack of proper balance between food, exercise and insulin. Severe attacks were prone to occur in patients who were overeating and attempting to control their glycosuria by increasing doses of insulin. A young school teacher had done this till he took 110 units as his morning dose; he collapsed in class on Wednesday morning and in spite of treatment was unable to converse intelligently till Friday evening, and had no memory of events till Saturday morning. It was well to bear in mind that hypoglycæmia could occur in diabetics not taking insulin, especially in mild cases in which treatment was by the old method of preliminary starvation, and sometimes in the case of juveniles at the onset of the disease.

Dr. Wilson then said that brain and heart required a liberal supply of glucose for normal working. This need would be accentuated if there was interference with blood flow, as in coronary disease or cerebral atherosclerosis, or if other substances were present which interfered with tissue oxidation, such as general anæsthetics or alcohol. Hypoglycæmia should therefore be avoided in the elderly and in patients suffering from coronary disease or hypertension, especially during anæsthesia. A liver well stored with glycogen was a source of supply when the blood sugar was depleted. A diet of adequate caloric value and a not too limited allowance of carbohydrate would provide this glycogen. A balance had to be achieved between food, exercise and insulin, and on days when more exercise was taken the amounts of food had to be increased. Long periods without food were to be avoided, especially when protamine zinc insulin was being used. With regard to treatment, Dr. Wilson said that food should be given at once; this would result in recovery in fifteen to twenty minutes, except in severe cases, or when pyloric spasm was present. Ten grammes of carbohydrate were usually enough, and it was unnecessary to keep on offering the patient drinks sweetened with glucose. To those who refused food, or who vomited, adrenaline or pituitrin might be given hypodermically. In severe cases, a sterile 25% solution of glucose might be given intravenously, and ampoules containing 25 cubic centimetres of this solution were readily obtainable.

The Raised Renal Threshold.

Dr. W. E. Fisher discussed the raised renal threshold. He said that in a standard work on physiology one might find some such statement as the following: "Any excess of sugar in the blood above 0·17% is excreted by the kidney. This percentage is often referred to as the 'renal threshold'." Such a figure had been arrived at as an average from many series of investigations, which showed that in the majority (80%) of healthy persons the threshold lay between 170 and 190 milligrammes *per centum*. The full truth of the matter, however, was more complex than this. The same investigations showed that in the remaining 20% of healthy persons the renal thresholds were about equally distributed above and below normal. In three series the full ranges of readings were 140 to 240, 114 to 231 and 99 to 228 milligrammes *per centum*. On this basis of the normal population it might be expected that at least one diabetic patient in ten would have a raised renal threshold. Dr. Fisher's experience at the Diabetic Clinic at Sydney Hospital gave him the impression that the incidence among a diabetic population was higher.

Similar investigations had shown that elevation of the renal threshold was sometimes fixed and sometimes variable, and that variation might occur in association with several factors. One of these was diet; it was quite an ancient observation that in the same patient the blood sugar level might rise to 301 milligrammes *per centum* without glycosuria, after the ingestion of white bread, while after ingestion of 100 grammes of glucose sugar appeared in the urine when the blood sugar had reached a concentration of only 186 milligrammes *per centum*. Another factor was disease of the kidneys, which would be discussed later; and quite recently it had been shown that the threshold might vary in response to the use of insulin and to different types of insulin. There was even evidence that a threshold might vary in the one patient from hour to hour. The physiological basis of this mechanism was still obscure. Current opinion held that normally sugar passed through the glomerulus in the same concentration as that in the blood, and that its absence from the urine was due to reabsorption in the tubules. Where the change took place that resulted in elevation of the threshold was not clear. The characteristic histological change in the diabetic kidney, which was also found in all forms of glycosuria (even in phloridzin poisoning, in which the blood sugar level was low), was a deposition of glycogen in the epithelium of Henle's loops. This was so common that it was doubtful whether it could be regarded as the basis of a condition occurring only in a minority of patients. There were rarer changes, such as the deposition of glycogen in the convoluted tubules, or even in the glomeruli; but Dr. Fisher knew of no attempt to correlate histological findings with the threshold, only with the level of blood sugar. Clinically, there was much evidence that alterations of the threshold might be associated with kidney disease, but it was conflicting. Blood sugar levels of 217 milligrammes *per centum* without glycosuria had been reported in acute nephritis, while glycosuria had been reported accompanying a normal blood sugar level in patients with nephrosis. The customary tests of renal efficiency were too crude for an apparently normal result to be taken into consideration in this connexion.

Dr. Fisher went on to say that probably everyone was now aware that the presence of sugar in the urine did not necessarily mean *diabetes mellitus*; but it was not so generally taken into account that sugar-free urine did not exclude the possibility of diabetes. On several occasions in the previous two years, warned by the presence of xanthoma or suspicious of an unexplained neuritis or loss of weight, Dr. Fisher had obtained a typically diabetic response to the glucose tolerance test when the patient's urine was sugar-free on routine testing. Dr. Fisher then referred to a patient whose glucose tolerance curve was a good example of the fact that the accurate correlation of the blood sugar level with that of specimens of urine as they were usually passed was not easy. More important in his opinion than this pitfall of diagnosis was the significance of a raised renal threshold in treatment. He then quoted figures to show that despite relatively satisfactory responses to urine tests, the patient

had maintained an abnormally high level of sugar in the blood for months. Should the physician be satisfied with sugar-free urine, regardless of the level of the blood sugar? Or should he aim at maintaining the blood sugar between the limits of about 100 and 180 milligrammes *per centum*? Dr. Fisher had put the question to four physicians, and their answers were summarized in the following way:

"A": Yes.

"B": Ideally, yes; but in practice it is too difficult and too expensive.

"C": In healthy young patients, yes; in elderly, arteriosclerotic patients, be satisfied with a sugar-free urine.

"D": Certainly not. The raised renal threshold is a compensatory mechanism with which we interfere at the patient's peril. Consider those cases in which the sudden fall of blood sugar is associated with cardiac pain and embarrassment. It is comparable with the necessity of high blood pressure to overcome the increased peripheral resistance in hypertensive heart disease.

In support of "A", it might be pointed out that an upper limit of 180 milligrammes *per centum* was apparently nature's ideal, or why was there any threshold at all? Even healthy patients with raised thresholds gave responses to the glucose tolerance test which were within normal limits. Again, in the case of that majority of diabetic patients who had normal thresholds, it was the implicit aim of the physician to keep the blood sugar between normal limits when he strove to keep the urine sugar free. Further, it was certainly his aim, whatever the renal threshold, when he was faced with such complications as sepsis and gangrene; if then, why not always? In reply to "B" it could be said that if a blood sugar level within normal limits was the ideal, why should they not strive for it? It was not difficult, and, although at the start it was admittedly more expensive, once stabilization had been achieved, only a periodical check by blood sugar estimation should be necessary if the patient was sensible. If he was not, no regime would meet with success. Answer "C" suggested that to strive after normal blood sugar levels in the case of an elderly patient with a raised renal threshold was to lock the door after the horse had gone; this begged the question whether the horse existed, and Dr. Fisher would deal with that aspect in contesting "D". First, he admitted that cardiac distress might follow hasty lowering of the blood sugar level; it did not always do so. In passing, it might be said that the comparison with high blood pressure would not hold. Recent surgical attacks on hypertension, deplorable as they would ultimately be considered, had proved incontestably that it was possible to set an established high pressure at a lower level with benefit, not danger, to the patient.

Dr. Fisher finally dealt with the real problem raised by answer "D" and implied in "C". Did an abnormally high blood sugar level in itself cause harm? Obviously, except in the presence of infection, it carried with it no immediate danger. Did it, then, promote the development of damage over a period—as, for example, the vascular changes? There were some recent grounds for such an hypothesis. (i) The concentration of sugar in connective tissue closely approximated that in the blood; (ii) biopsies of the skin of diabetics with high blood sugar levels had revealed œdema and a basophilic tendency, which had been compared with the state of the intima in the early stages of arteriosclerosis. Such damage might well produce permeability to the waiting lipoids, the association of which with vascular changes was well known, though it was unlikely that they could harm a healthy intima. For further evidence of the close relationship of blood sugar concentration to tissue change they had only to remember those changes in the refractive index of the optic lens which could produce so much confusion. Dr. Fisher therefore made the following suggestions: (i) Elevation of the renal threshold for sugar, to be expected in one out of every ten diabetic patients, if not more, was sufficiently common to merit consideration. (ii) The mechanism of its production was obscure, and its association with renal disease, while not apparently essential, was frequent enough to make it advisable to search for the one when the other was evident. (iii) To remember the possibility of its presence would remove a pitfall of diagnosis. (iv) In treatment they should aim at maintaining within normal limits the blood sugar of patients with raised thresholds, just as they did that of patients with normal thresholds. (v) If the patient was cooperative this was not difficult, only a little more expensive. (vi) The reduction of high levels of blood sugar, masked by a raised threshold, to normal, could be carried out without harm to the myocardium. (vii) In view of the occasional variability of the renal threshold, it should be checked by blood sugar tests from time to time. (viii) Support might be adduced for the view that high blood sugar levels over a long period tended to the production of tissue changes, notably in the blood vessels.

Standard Diet Lists.

DR. W. L. CALOV spoke on the subject of diet lists. He said that it was necessary first to have some understanding of what was meant by a standard diet list in diabetes. (i) It might be a list made out ready to be handed to the patient, the medical attendant having merely to decide on the caloric value (for example, Ingram's system). (ii) It might be arranged so that any standard portion represented a certain number of Calories, the diet being prescribed as a certain number of these portions (for example, Lawrence's "line-ration" system). (iii) It might consist merely of tabulated quantities of a number of foodstuffs of certain caloric value, and containing certain amounts of carbohydrate, protein and fat (for example, Joslin's system in use at the New England Deaconess Hospital). Of these various systems Lawrence's was perhaps the most adaptable; but it had the disadvantage of demanding some slight exhibition of intelligence from the patient. The medical attendant might prescribe the correct number of "lines" for each meal, and yet the patient would be confused. Further, the prescription of a "line-ration" diet required the exercise of the medical attendant's mathematical skill, for the number of lines required had to be calculated from the carbohydrate content of the black lines and the protein and fat content of the red lines. This was not beyond the capacity of most medical practitioners; but it was apt to cause some distress to those not gifted at arithmetic. Each black line represented ten grammes of carbohydrate (40 Calories) and each red line 7·5 grammes of protein and 9·0 grammes of fat (111 Calories). If the medical attendant wished his patient to take a diet containing carbohydrate, protein and fat in the proportions of 15:7·5:9, he ordered three black lines to every two red. A simple calculation revealed that the caloric value of the carbohydrate in proportion to the caloric value of protein and fat combined was 60:111; therefore, if the total number of Calories required was divided by 171, the result would be the number of red lines necessary. The number of black lines could then be readily calculated. The same procedure was applicable whatever proportions were adopted, provided that the ratio was calculated from the caloric value of a single red line (111).

Dr. Calov went on to say that if medical practitioners were determined to make up their own diet lists from first principles, their mathematical problems became quite unpleasant obstacles. There were some amongst them who were capable of, and possibly enjoyed, "dashing off" a complicated diet list in an actuarial manner; but Dr. Calov thought that they were in a small minority. No doubt the planning of meals was a joy to the industrious housewife, untrammelled by considerations of caloric requirements and ketogenic:antiketogenic ratios; but to the average medical practitioner it was no joy. Unless they prescribed each meal fully, they were shirking their problems and leaving their solution to the patient. This was unfair.

The most satisfactory dietary scheme was the one Dr. Calov had first mentioned. The patient was given a list of the articles of food and the quantities he was to take at each meal. There was no room for doubt, and there was no necessity for calculation. The patient merely consulted his list and prepared his meal accordingly. These lists might be prepared by the medical attendant himself if he was fond of mathematics, and kept by him for use as standards; or he might use the lists that had already been published by Ingram. If he thought that any individual patient required more or less protein, carbohydrate or fat, he would find little difficulty in making the desired adjustment to the list. It was to be noted that in Ingram's scheme the carbohydrate content became proportionately higher (in other words, the ketogenic:antiketogenic ratio diminished) as the caloric value increased. In the lists of low caloric value the proportions of carbohydrate, protein and fat were roughly equal; in the 2,200-Calorie diet the proportions were roughly 175 grammes of carbohydrate to 98 of protein to 95 of fat ($F.A : G = 0{\cdot}54$). The latest publication included lists for patients taking modified insulin; in these provision was made for a greater number of meals during the day, to prevent hypoglycæmia.

The advantages of these diets were many. The ease of prescription was the first to commend itself to medical practitioners. The only mental exertion required was in the decision as to what the caloric value of the patient's diet should be; the prescription consisted in handing the patient

a typewritten or printed sheet. A further advantage in Australian practice was that they were based on an analysis of Australian food materials. The patient was allowed a choice of three different breakfasts, three different lunches and three different dinners. If one was mathematically inclined, or even if he was a cribbage player, he would be able to calculate rapidly that the patient had 27 different combinations of meals to choose from. If the patient had normal intelligence he could vary his diet by making use of his list of substitutes for bread, and if he was more intelligent and also experienced in dieting, he could add still more variety by using the tables of equivalents.

In a busy out-patient department or diabetic clinic, unless it was staffed by an army of dietitians, standard diets were essential. In the hurly-burly of general practice they saved the medical attendant a great deal of time while still being advantageous to the patient. In the calmer atmosphere of consulting practice the physician would find them equally valuable.

Diabetes Mellitus: The Care of the Feet.

DR. W. W. INGRAM spoke on the care of the feet in *diabetes mellitus*. He said that the general use of insulin and a better understanding of the principles underlying the treatment of *diabetes mellitus* by medical practitioners had greatly increased the duration of life of their diabetic patients. Arteriosclerosis had therefore replaced coma as the most frequent cause of death in diabetes. The arteriosclerosis seemed to be related more to the age of the patient than to the duration or severity of the disease. For instance, during the previous eighteen months 35 diabetic patients with serious foot complications partially attributable to the effects of arteriosclerosis had been admitted as in-patients to the Royal North Shore Hospital, and their average age was sixty-seven years. The youngest was aged fifty-eight years and the oldest eighty-three years. They therefore fell within the age group in which arteriosclerosis was frequently found.

In diabetes the arterial degeneration mainly affected the coronary arteries and the arteries of the lower limbs, and in these were found thickening of the intima either alone or superimposed upon medial calcification. In the smallest arteries was found an obliterative endarteritis with almost complete obliteration of the lumen. Consequently the nutrition of the tissues of the feet was defective and their resistance to infection was lowered. Furthermore, the arterial changes were frequently associated with some degree of neuritis leading to numbness and anæsthesia. The skin of the feet of elderly diabetics was therefore unduly sensitive to injury, and what at first appeared to be slight damage might lead to disastrous results. Of the 35 patients mentioned, five had a rapidly spreading moist gangrene following an injury, the effect of which was neglected for some days before they sought relief. Three of these patients died, one before operation could be performed, and all the others had the leg amputated above the knee. In six cases a partial amputation of the foot was performed and in four others a toe or part of a toe was allowed to separate and slough off. Seven had severe tinea infection, six had perforating ulcers of the foot and the remainder had commencing cellulitis with pregangrenous areas resulting from the cutting of corns, pressure from badly fitting shoes and minor injuries. In nearly all cases diabetic restrictions had been neglected. All or nearly all of these "accidents" could have been avoided by proper foot hygiene and by the adoption of measures to improve the circulation of the legs.

All diabetic patients who showed evidence of arteriosclerosis should receive special instruction in the care of the feet. They should wash their feet daily with soap and tepid water. The feet should be thoroughly dried and powdered, and if toes tended to overlap they should be kept separated by lamb's wool inserted between them. Each night before the patient retired the feet should be gently massaged with olive oil or "Lanoline". Bed socks should be worn and hot-water bottles should never be placed near the feet. Properly fitting socks had to be worn, and they should be changed daily. Socks which were darned should be discarded and silk stockings should not be worn next to the skin. The shoes had to be well fitting and should be roomy at the toes and fit snugly round the heel. Metal arch supports should not be worn. Patients whose feet were deformed from swollen joints or callus formation should be referred to the orthopædic department and fitted with orthopædic shoes. This had been done in several cases at the Royal North Shore Hospital, with most satisfactory results. The cutting of corns and nails should never be done by the patient, who in most cases had defective eyesight. They should be dealt with by a trained chiropodist or by a trained nurse attached to a diabetic clinic. Tobacco smoking should be discouraged, since nicotine caused spasm of the peripheral vessels leading to further deterioration of the circulation. If the foot was injured, however slightly, smoking should be prohibited and the foot given complete rest. It was sometimes very difficult to prevent old men from having a few pipes of tobacco; but there was no doubt whatever that lesions of the feet healed much more quickly if smoking was prohibited. Alcohol caused vasodilatation of the peripheral vessels, and a "night-cap" of whisky would often relieve night cramps. It should be given once or twice daily when the foot was injured. Irving Wright advocated keeping the patient slightly inebriated during the critical period in impending or actual gangrene. Simple exercises for increasing the flexibility of the muscles and improving the circulation should be prescribed, such as Buerger's exercises. The patient lay on his back in bed and the legs were elevated on pillows to an angle of 45° to 60°. They were left in that position for one to three minutes. They were then lowered over the edge of the bed for three to five minutes and thereafter rested in the horizontal position for five to ten minutes and covered over. This exercise should be repeated four or five times, at least once and preferably twice a day. Muscle cramps could be relieved and the circulation of the feet and legs could be improved by the use of the pressure suction boot or by intermittent venous occlusion; but they should not be used if inflammation was present.

In all foot complications in diabetes an orthopædic surgeon should be consulted early. The foot should be radiologically examined for osteomyelitis and calcification of the vessels, and measures should be taken to render the patient's urine sugar free and to improve the circulation. When the skin was broken or injured, strong antiseptics, such as iodine, should not be applied, as a chemical burn might result. The area should be gently washed with soap and water and sterile gauze soaked in spirit should be applied. Dr. Ingram had used a 1% solution of picric acid with good results, also cold eusol compresses. All such injuries should be immediately reported and carefully observed by the medical attendant. Perforating ulcers that underlay the heads of the metatarsals began as ulcerations in preexisting calluses. These lesions were not painful and were neglected by the patient. The skin was cornified and had a poor blood supply; this predisposed to infection and slow healing. These areas resulted from pressure from badly fitting shoes and socks. The best treatment for these ulcers was early excision. Osteomyelitis developed early and with few symptoms, and so was frequently missed. For this reason it was important to examine the foot radiologically at an early stage, and where a discharging sinus was present gently to probe for roughened bone. The early diagnosis of osteomyelitis was important, because conservative treatment was valueless and might jeopardize the toe or even the foot. Gangrene might be either dry or moist. The latter was the more dangerous, as it was always accompanied by infection. Dry gangrene resulted from the cutting off of the blood supply to a toe or part of a toe, and was preceded by signs of insufficient circulation—cramps and pains in the feet and calves. In some cases the pain was very severe and the foot was hypersensitive, the slightest touch causing severe pain; in others sensation was diminished, with consequent danger of trauma such as burns. Gangrene should be treated conservatively; the part should be kept dry, spirit should be applied and a sterile dressing should cover the lesion. General measures were instituted to improve the circulation, and when the line of demarcation appeared the patient should be allowed to exercise for short periods. Moist gangrene required immediate surgical attention, either by incision and drainage or by amputation. Sulphanilamide or sulphapyridine should be given; but as they tended to produce acidosis, they should be given along with sodium bicarbonate. Lately Dr. Ingram had been using the infra-red lamp in the treatment of spreading cellulitis, and in his opinion the results had been improved. As Joslin pointed out, if the skin of the feet was kept perfectly clean, moist gangrene should not develop. All elderly diabetics should therefore be instructed in the care of the feet, and they should be warned: (i) to keep the feet scrupulously clean; (ii) not to open blisters with needles or to use sharp instruments on corns; (iii) not to use strong antiseptics, put their feet in hot water, or use hot-water bags on the feet; (iv) not to wear tight garters or to sit with the knees crossed; (v) not to wear tight shoes or stockings or metal arch supports; (vi) not to bandage the feet or legs tightly or to use adhesive tape. In conclusion, Dr. Ingram said that it was impossible to cover the whole field in a short paper; but if all elderly diabetic patients were to carry out these simple measures, fewer foot complications would be seen.

Problems Peculiar to Juvenile Diabetics.

DR. E. H. M. STEPHEN said that he would speak of the special points of the treatment of diabetes in childhood. A suitable beginning was a short résumé of the diet. It had proved wisest, in the arrangement of the diet for the diabetic patients at the Royal Alexandra Hospital for Children, to allot their Calories by a consideration of age rather than of body weight, for the following reason: an undernourished child remained undernourished if fed on the plan of so many Calories per kilogram of body weight. On the system used, the children maintained and gained weight satisfactorily, and proved rather more resistant to disease than the average child. The age and the Calories given were the following:

Age.	Calories.
1 to 2 years	720 to 1,100
2 years	1,100
3 years	1,200
4 years	1,300
5 years	1,400
6 years	1,500
7 years	1,600
8 years	1,700
9 years	1,800
10 years	1,900
11 years	2,000
12 years and upwards	2,100 to 2,400

Age and weight had been combined for the determination of the protein allowance; the younger children received a larger allowance than the older ones. At least half had to be first-class protein.

Age.	Protein.
1 to 3 years	3·5 grammes per kilogram of body weight
3 to 5 years	3·0 grammes per kilogram of body weight
5 to 15 yeass	2·5 grammes per kilogram of body weight

The carbohydrate allowance was 30% to 40% of the total Calories.

With regard to fat, 2·3 to 3·0 grammes per kilogram of weight were a suitable quantity. Some children tolerated fat indifferently, so modification was necessary. In most cases it was difficult to provide an adequate diet unless the high caloric element, fat, could be used with some degree of liberality. In sickness of any sort, fat was reduced somewhat disproportionately to protein and carbohydrate. An instance typical of this arrangement of diet was that of R.G., a boy, aged twelve years, whose weight was 92 pounds. He received a total of 2,056 Calories, made up 199 grammes of carbohydrate, 93 grammes of protein and 98 grammes of fat. He had been a patient for a number of years, and had made steady progress. Children aged ten years received approximately 1,900 Calories, and this amount usually ensured satisfactory progress for the next three or four years, especially in the case of girls.

In the treatment of the precomatose, the child was given 560 Calories provided by the administration of fruit juices supplemented by 10% glucose solution when sufficient juices were not available. In twenty-four hours 300 Calories more were given by the administration of milk, and daily additions were made with the inclusion of vegetables, meat and eventually porridge and milk puddings. For comatose patients intravenous injections of saline solution, up to 20 ounces, were used; the bowel was washed out and often the stomach as well. Forty units of insulin were given, then 20 units in two hours and then every four hours with fruit juices as mentioned above; it was necessary to be guided by estimations of the blood sugar and by the results of urine tests. Dr. Stephen said that he gave these figures as a general guide, though individual cases might easily not conform to this rule.

Dr. Stephen was cautious about the use of glucose tolerance tests for child diabetics, especially if acetonuria was pronounced and persistent. A few days of careful watching of the patient and preliminary adjustments represented a sound policy. He had adopted this view after experience had taught him its wisdom.

It had proved difficult to use retard insulin preparations at the hospital clinic, and more security had been achieved by the use of ordinary insulin. For an older child Dr. Stephen had found insulin retard at 6 p.m. successful in avoiding hypoglycæmic turns through the night. The clinic had aimed at securing one positive response to the test for sugar in the twenty-four hours. Only by such a manœuvre could one avoid hypoglycæmic occurrences.

The stabilization of child diabetics presented unusual difficulties. The unstable nervous system of childhood appeared to a pronounced degree once children were admitted to hospital. Secondly, the amount and type of exercise they were used to in home surroundings could not be imitated in hospital. Dr. Stephen had had the experience of a child in whose urine sugar and ketone bodies appeared even when she was kept out of bed and escorted on every expedition the nursing staff executed. On her return home, receiving a diet and insulin dosage as in hospital, she was free from glycosuria and ketonuria. It was perhaps possible to determine the amount of fat these children could tolerate, but finality was not obtainable and adjustments of insulin dosage and diet had to be carried out on their return home. Excitement could affect the child and produce a state of hyperglycæmia or hypoglycæmia. As an instance of the effect of excitement, a patient of Dr. Stephen's, aged six years, was driven to Mascot to see her father arrive by aeroplane. She signalized this triumphant feat by a heavy reduction of Fehling's solution. The same child became hypoglycæmic on witnessing the presentation of prizes to her kith and kin at a boys' preparatory school.

Dr. Stephen said that he had a prejudice against the use of grapes. It was a prejudice easily accounted for, as two fatalities had occurred after what he believed was an orgy of grapes. It might be that grapes were more alluring than other articles of diet, or that there was some unusual feature in connexion with the assimilation or storage of the carbohydrate they contained.

Dr. Stephen then quoted several cases. A boy, aged ten years, who in the first instance gave the glucose tolerance curve of renal glycosuria, later proved himself a true diabetic. With treatment by insulin and diet, from a living skeleton he became a robust Irish athlete. A bicycle ride procured his admission to the Royal Prince Alfred Hospital, as he became hypoglycæmic and unconscious on Newtown railway station. A girl, aged twelve years, could not be preserved from hyperglycæmia by dietetic adjustments and 230 units of insulin *per diem*. Her pancreas proved almost destitute of islands of Langerhans. Indulgence in grapes terminated the unequal struggle. A boy, aged nine years, had sugar-free urine for weeks even without insulin, but failed to thrive and was found to have a high renal threshold for sugar. This peculiarity may have accounted for his demise in another hospital.

In conclusion, Dr. Stephen made several suggestions: (i) That authorities in colder countries than Sydney arranged diets with a higher caloric content than was necessary or advisable in this country. (ii) That one should be sensitive about fats; in any difficulty it was wise to reduce them, especially for younger children—the older children tolerated them twice as well. (iii) That adrenaline should always be at hand for the diabetic child; for a patient in hypoglycæmic unconsciousness a hypodermic injection of adrenaline might prove invaluable and quick in its action; the stomach would probably vomit glucose, even when it was introduced by tube, and adrenaline might obviate the necessity for the intravenous use of glucose. (iv) That if the patient was spending the day in bed, the Calories of the diet should be reduced by a quarter; if pyrexia was also present, they should be reduced by one-third, and in particular the fat allowance should be reduced, the insulin dosage being maintained at its usual figure.

The Relative Merits of Soluble and Insoluble Insulin.

DR. KEMPSON MADDOX spoke on soluble and insoluble insulin. He said that soluble, standard, regular or ordinary insulin had been in general use for over sixteen years, so that its remarkable merits had been adequately recognized. Its short period of action, however, resulted in irregular blood sugar control, particularly during the night hours. Attempts to combine insulin with various adsorbents which would release insulin more slowly from subcutaneous depots were relatively unsuccessful, until Hagedorn, of Copenhagen, found that a combination of insulin with a monoprotamine derived from fish sperm prolonged insulin action up to twelve hours. About that time Scott and Fisher, of the Connaught Laboratories at Toronto, found that several substances, of which zinc, bismuth and calcium were the chief, further delayed the action both of regular and of protamine insulin. The effects of a single injection of zinc protamine compound were found to last for as long as from forty-eight to seventy-two hours. Since June, 1936, the compound had been manufactured by many reliable firms, and was marketed in two strengths, containing 40 and 80 units of insulin to the cubic centimetre.

Dr. Maddox said that it was necessary to utter a warning at this point concerning the use of the adjectives "single" and "double" in reference to strengths of the compound. Actually the strengths available were double and quadruple those of standard or regular insulin. During the past four

years, the application of this compound to diabetic therapy had become firmly established, and it was now possible briefly to review the status of the insoluble as compared with the soluble insulin. As a result of the more general availability and wider literature concerning the zinc protamine compound, experience of the new insulin products was largely based on that obtained from practice with this substance. It had completely replaced protamine insulin at the diabetic clinic at the Royal Prince Alfred Hospital, and experience there with other types of retarded insulin had been too small to provide any opinion of value. Dr. Maddox said that he would give a brief description of the current reputation of two of these, namely, globin insulin and crystalline insulin, after which he would confine his remarks exclusively to the application of the zinc protamine compound.

Insulin was first prepared in a crystalline form by Abel in 1926. Sahyun stated that at pH 6 to 6·6 the crystals were less soluble than amorphous preparations, and so suggested that absorption might be slower. Conflicting clinical reports followed. Experimental work failed to reveal any great retardation. Marble and Vartiainan compared the respective effects of amorphous and crystalline insulin on both normal and diabetic persons. The results were very similar; a prompt and almost identical rate of fall in blood sugar level resulted. There appeared to be a very slight prolongation of action in the normal persons, and a slightly greater fall in the diabetics, when crystalline insulin was used; but the delay was too slight to be of clinical use.

Globin insulin was prepared by the addition of 38 milligrammes of globin and 3 milligrammes of zinc as zinc chloride to 1,000 units of standard insulin. The mixture was buffered to a pH of 6·1; 99% of the insulin was contained in the precipitate so formed. It had latterly been shown that at pH 4 a clear solution was obtained without any difference in clinical effect. After administration, insulin action began almost at once and reached a maximum seven to twelve hours later. Eighty to 120 units had been used in a single dose. The same obscure variation in effect with occasional hypoglycæmic shock was seen with this as with other types of insulin. Allergic effects were rare. Opinion at present was that the substance warranted an extended trial, and had a place as an intermediate type of depot insulin. Nevertheless, to simplify treatment for patients and physicians alike, it was advisable to decrease rather than to increase the number of types of insulin on the market. At the present stage it seemed desirable to limit these to (*a*) a rapidly acting insulin, perhaps crystalline, and (*b*) a slowly acting variety like protamine zinc insulin.

With regard to the relative merits of zinc protamine insulin, Dr. Maddox said that it was hoped at first that a type of insulin with such a long period of activity would, in a single daily injection, alone supply all exogenous insulin requirements, and by a steady release of active hormone throughout the twenty-four hours would closely mimic the normal islet secretion. It was anticipated that the steep peaks in the twenty-four-hour blood sugar curve of the labile diabetic would be smoothed out, and that the problem of the "insulin waster" would be largely eliminated. These expectations were quickly proved to be false. Attempts to produce virtual disappearance of glycosuria by mounting quantities of the compound resulted in severe, sudden and often alarming hypoglycæmic shock sixteen to twenty hours later, from which the patient was extricated with slowness and difficulty. On the other hand, in the case of diabetics requiring no more than 20 to 30 units of insulin per day, administration of the insoluble form acted like a charm. These good results were obtained irrespective of the hour of administration, which was a real boon to senile patients with mild diabetes, who, unable to inject themselves, were visited at some time in the daily round of the district nurse. Occasionally a visit every second day sufficed. It was a privilege to pay tribute to the splendid work of this organization, whose members, through the advantages of this form of insulin, were able to bring the life-preserving benefits of insulin therapy to the homes of the old and weak.

The realization that control of more severe diabetes by a single daily dose of zinc protamine compound was often fraught with inconvenience and even danger tended to disparage insoluble insulin, and two reactions followed. The first could be illustrated by Dr. Maddox's own feelings two years earlier, when in an article on this subject in "The Royal Prince Alfred Hospital Year Book", he had written:

> After an extended trial of this substance on selected patients, representative of all clinical classes of diabetics, we, at this clinic, have come to the conclusion that the compound is best applied to the control of mild diabetes. Where, from the severity of the diabetic state, or from the lability of the daily fluctuations of blood sugar, two or more hypodermic injections of insulin in the twenty-four hours are called for, little is to be gained from the introduction of the compound from the patient's point of view.

The second reaction among diabetics, which embraced a larger following, called for a continuance of the attempt to fulfil the early promise of the retarded insulin—namely, that by a single thrust of the therapeutic dagger, the diabetic dragon could be laid low for another twenty-four hours. To accomplish this and yet to protect the patient from the stealthy serpent of hypoglycæmia, some revision of the criteria representing "satisfactory control" of the diabetic state was demanded. A more generous view as to the harmlessness of the persistence of glycosuria had become a common doctrine, especially in the United States of America. In fact, the statement was frequently made that so long as the patient maintained weight and was free from symptoms and ketosis, the excretion of even as much as 100 grammes of sugar in a day in the urine might actually be disregarded. No real proof, it was said, had been forthcoming to the effect that hyperglycæmia accelerated cardiovascular degeneration or predisposed the patient to infection. In fact, continuous glycosuria was desirable and afforded protection from insulin reactions. Armed with this comfortable conclusion, it was possible in by far the majority of cases to "succeed" with single daily doses of zinc protamine insulin alone.

Whilst Dr. Maddox was prepared to admit that glycosuria occurring not more than once a day, or to a higher concentration than 1% of sugar (10 to 20 grammes, total daily excretion), had to be accepted as the best that could be achieved with certain resistant individuals, especially children, he could not forget the poor resistance to infection, the bouts of pruritus, the ready ketosis or the multiple attacks of coma which such "resistant" or "difficult" patients frequently exhibited. Further, he reminded those present that they had all seen diabetics gain in weight during uncontrolled phases of their disorder, so that that criterion could not be relied upon. The altered physical properties of hyperglycæmic blood might also be harmful. Atherosclerotic lesions occurred early in diabetic as compared with non-diabetic persons. The cause of this was unknown. Which, if any, of the components of the diabetic biochemical complexes were particularly responsible for this degeneration was unknown. It seemed reasonable, therefore, to aim at as complete a restoration towards the whole metabolic normal as their remedies permitted, the reduction of hyperglycæmia included.

The truth probably lay half-way between these two schools of thought in regard to the value of the insoluble compound. Dr. Maddox's own views had changed to the extent that he used this substance whenever possible, alone in mild diabetes, and combined with supplements of standard insulin in the more severe case. The plotting of the twenty-four-hour blood sugar curves and daily estimations of sugar output had convinced him that, in the latter cases, the mean blood sugar level was lower than when either type of insulin was used alone. Glycosuria, since it had to occur in certain instances, was preferable to insulin reactions, which ruined the patient's confidence in his chief ally.

The combination of delayed insulin with standard insulin, or delayed insulin alone, had several advantages, as compared with the use of standard insulin alone: (*a*) The number of injections was often reduced. (*b*) Nocturnal hypoglycæmia was prevented. (*c*) The diabetic life was less hurried and meals did not need to be taken strictly on time. (*d*) The inveterate diet breaker was better protected from the consequences of his indulgence.

Dr. Maddox then discussed diet and exercise. He said that the diet, particularly the carbohydrate fraction, taken with zinc protamine insulin, required some rearrangement as compared with that usually adopted for use with standard insulin. The original plan was to attempt to secure a steady inflow of exogenous carbohydrate to the liver by the provision of five equal meals in the twenty-four hours, and in general this principle was still adhered to. Experience had shown, however, that a substantial supper, mainly of carbohydrate (30 to 40 grammes), should form an integral part of any scheme for diet partition. This to some extent protected the patient against nocturnal hypoglycæmia. Too much should not be expected from diet rearrangement. If hypoglycæmia became troublesome, a fresh adjustment of insulin dosage was called for. Hypoglycæmia after exercise was more readily induced when protamine zinc insulin provided most of the insulin taken, and an anticipatory meal of

carbohydrate before deliberate exercise or sport was undertaken is distinctly advisable. Workers, such as truck drivers, who might prejudice public safety by an attack of hypoglycæmia, were often better treated by standard insulin.

Dr. Maddox said that he had formed certain conclusions as to the best technique for the administration of the zinc protamine compound. It had been found at the diabetic clinic at the Royal Prince Alfred Hospital that in mild cases control was achieved by a single injection of about 20 to 25 units, in moderate cases by 20 to 40 units together with a supplement of standard insulin averaging 10 units, given together before breakfast, and in more severe cases by 40 to 50 units of retarded insulin with a morning and evening supplement of 10 to 15 units of regular insulin. These figures were, of course, only approximate, but they represented the findings in a large number of cases. The new patient, unless threatened by ketosis, was ordered the anticipated final dose of zinc protamine insulin, which he took for a week; at that time, if the urine passed into the bladder during the first hour after waking was sugar free, he was carefully interrogated for evidences of hypoglycæmia. He might have suddenly awakened to find himself confused, weak and sweating; he might have early morning headache, difficulty in waking up or behaviour phenomena such as irritability and naughtiness. (The last were more common in children.) If such complaints occurred, the dose of insulin was reduced by three units at a time. If sugar was present in the "shaving" specimen of urine, the dose was increased by a similar amount, but not under a four-day interval, owing to the cumulative nature of the preparation. A 6 a.m. blood sugar estimation was the counsel of perfection, but was seldom practicable. Urine tests one hour and a half after each meal gave an indication of the remainder of the twenty-four-hour curve, and when the early morning hyperglycæmia was controlled, they showed where supplements of standard insulin were required. These were begun in doses of about eight units, and no more than two units were added at a time, as the hypoglycæmic effects of standard insulin were enhanced in a diabetic already receiving zinc insulin. When the "coarse" control had reached the stage at which nearly all specimens were sugar free, and the patient was free from hypoglycæmic symptoms during an average day's activity, an estimation of the sugar in a twenty-four-hour specimen of urine was desirable. If the amount exceeded 10 to 20 grammes, a review of insulin and diet arrangement was called for, and by a "fine" balancing of these, a further improvement was usually possible. Finally, the patient was required to test the urine only once a day, but at a different hour each day of the week—on waking, one hour later, and an hour and a half after each meal. The two most important of these were the early morning and the "after tea" specimens. Patients changing from standard to zinc protamine insulin should be warned that glycosuria usually returned for a few days, and no alteration in dosage should be made in the first week unless nocturnal hypoglycæmia intervened. The number of injections could nearly always be reduced from three to two per day when patients were changed to the newer insulin; thus, 76 patients were saved 116 injections. The question of whether a higher or lower daily quantity was required after the change was by comparison a relatively minor matter.

The actual administration of both types of insulin together did not require a special double-barrelled syringe, nor were two separate injections necessary. The zinc protamine insulin was given first, and the needle was left *in situ*. The syringe was disconnected and filled with regular insulin through a second needle. This in turn was disconnected and the regular insulin was administered through the first needle, which was withdrawn as far as the skin and then pushed back in a new direction. Allergic phenomena were uncommon with zinc protamine insulin. It was high time that it was manufactured in Australia, but only if the same refinement was maintained as characterized the imported product. In conclusion, Dr. Maddox said that there was no time to speak of the value of zinc protamine insulin in coma, in preparation for operation and for children. But it was his firm belief that whenever insulin was required, they should endeavour to supply a proportion of it at least in the form of retarded insulin, being mindful of the fact that zinc protamine insulin did not fail to fulfill its promise if more than one insulin injection a day was required, and providing the maximum dose of the compound was kept below 50 units a day.

DR. O. A. DIETHELM said that those present owed a debt of gratitude to the speakers for their very complete exposition of the subject. He referred first of all to the fact that pronounced reactions occurred, exactly similar to hypoglycæmic attacks, when very large doses of insulin were given, even though the blood sugar content was within normal limits. That should be remembered when large doses of insulin were given. Dr. Diethelm then referred to protamine zinc insulin; he said that it marked a distinct advance in therapy. Two of the greatest advantages of this compound were, first, that with its use serious hypoglycæmic reactions were less likely to occur, and secondly, that the reactions that did occur were often much more easily recognized and milder, in the form of headache, nausea and malaise. When once the patient had had one of these attacks, the early mild symptoms could easily be dealt with, and were not so disturbing as the more acute symptoms of temporary hunger, nervousness and sweating which signalized the reactions of ordinary regular insulin. The great advantage was the mildness of the symptoms which patients soon came to recognize easily themselves, even though at times the reactions might be more severe. A further benefit obtained by the use of protamine zinc insulin was in surgery, where its constant slow reaction when given before operation in the morning protected the patient against the possibility of an insulin reaction during the anæsthesia. Moreover, large quantities of carbohydrate and glucose could be given and utilized both before and after operation; this was especially useful in thyreotoxicosis. Serious reactions that formerly occurred in large operations were less likely to occur, especially when a dose of glucose had been given intravenously before the patient went back to bed. Dr. Diethelm then referred to arteriosclerosis in diabetics. He said that most of those present had certainly had experience of elderly arteriosclerotics. The patients were given a carefully balanced diet, and the amount that they would need in twenty-four hours was worked out; but in spite of everything that was done, it was found that even if the carbohydrate content of the diet was cut down, they always tended to excrete a little sugar in the urine; and to achieve stabilization it was often necessary to give large doses of insulin. Dr. Diethelm thought that these patients did better and felt better if they were allowed a good maintenance diet preferably without insulin, or at least moderate daily amounts even if they did excrete a little sugar, provided their blood sugar level was not too high (not more than 180 milligrammes *per centum*). In many cases it would be found most difficult to produce a normal blood sugar curve and to render the urine sugar free; even then, the patients were very miserable and devoid of all energy. Finally, Dr. Diethelm said that since the introduction of protamine zinc insulin, skin reactions occurred more frequently; these took the form of atrophic conditions at the point where the insulin was injected, a local lipodystrophy, indurated areas and patches, in which reactions to insulin would be very variable. Allergic reactions were also much more common with zinc protamine insulin; they took the form of swelling, redness and tenderness. Dr. Diethelm had recently had a case in which the opposite occurred; allergic reactions occurred with ordinary insulin, but not with zinc protamine insulin. A patient, aged fifty years, was under treatment in the out-patient department. Various brands of regular insulin were tried, but she had intense allergic reactions every time. She was admitted to hospital and protamine zinc insulin was tried; no reaction at all occurred. Dr. Diethelm thought that in time patients who had severe reactions and were allergic to all forms of insulin would probably become desensitized.

Dr. F. Hales Wilson, in reply, said that he entirely agreed with what Dr. Stephen had said on the use of adrenaline. In reply to Dr. Diethelm, Dr. Wilson said that in his experience hypoglycæmic reactions were very much milder when protamine zinc insulin was used; at least, that was so when moderate doses were given. But he thought that with larger doses very severe reactions might develop and the onset might be insidious; the patient might not heed the warning because the attack might come on so silently. Dr. Wilson said that he was sceptical about the possibility of hypoglycæmic symptoms occurring in spite of high blood sugar levels; he had had no experience of such an event. Dr. Diethelm had referred to skin reactions; Dr. Wilson said that his experience had been similar. With regard to the patient who was sensitive to all brands of insulin except protamine zinc insulin, Dr. Wilson thought that that was an example of true insulin allergy; one injection of protamine zinc insulin was like a series of small injections which overcame the allergy.

Dr. W. E. Fisher said that he had to admit that he knew of no proof that persistently high levels of sugar in the blood were in themselves damaging; but he thought it possible that the underlying fault that they represented was damaging. But he admitted that in some cases the

phenomenon was attended with normal results, and one had to proceed carefully if one set about lowering the level of sugar in the blood. Yet even in the presence of myocardial damage, as had been shown in the case he had quoted, the lowering of the blood sugar level was not necessarily a cause of further damage.

PROFESSOR INGLIS, from the chair, on behalf of the New South Wales Branch, thanked the Section of Medicine, and particularly the speakers, for the excellence of their subject matter, and for the entertaining and picturesque way in which they had presented their papers. He said that the good attendance was in no small measure due to the work of the secretary of the section, Dr. Fisher.

A MEETING of the New South Wales Branch of the British Medical Association was held on October 24, 1940, at Saint Vincent's Hospital, Sydney. The meeting took the form of a number of clinical demonstrations by members of the honorary staff of the hospital.

Carcinoma of the Urethra.

DR. C. F. DE MONCHAUX and DR. NELL FARRAR showed several patients from the radiotherapy department. Their first patient was a female, aged fifty-four years, who had been referred to them in May, 1938, with an early carcinoma of the urethra. The lesion, which was proliferative rather than ulcerative, involved the urethral canal near its external orifice, and extension had occurred to the anterior vaginal wall. There were no palpable inguinal lymph nodes. Microscopic examination of a section of the growth showed it to be a squamous-celled carcinoma. This patient was treated by radiotherapy alone in the following sequence: X-ray therapy primarily to the urethral lesion was given in May, 1938; X-ray therapy to the primary focus and to both inguinal regions was given in July, 1938; and interstitial radium therapy was given in September, 1938, in the form of radium needles inserted around the urethral lesion. Two months later the urethral growth appeared to be healed and there was some slight contraction of the urethra. Three months later than this, however, there was some recurrence of the growth at the primary site, whereupon more X-ray therapy was administered locally (February-March, 1939). In May, 1939, definite improvement was noted, no growth being then visible or palpable. When the patient was reexamined in October, 1940, there was no sign of any recurrence and her condition was quite satisfactory.

Dr. de Monchaux and Dr. Farrar commented that epithelioma of the urethral lining was by no means common, but, being derived from squamous epithelium, it should respond well to radiotherapy. In the case under discussion a combined method of X-ray and radium therapy had been used, and the result had remained satisfactory for nearly two and a half years.

Hyperplasia of Lymph-Nodal Tissue.

Dr. de Monchaux and Dr. Farrar then showed two patients who provided good examples of hyperplasia of lymph nodal tissue. The lesions were two varieties of the so-called reticuloses, as described and classified by Robb-Smith in his article on "Reticulosis and Reticulo-Sarcoma", published in *The British Journal of Pathology and Bacteriology*, Volume XLVII, 1938. Both patients had been referred recently to the radiotherapeutic department, both were young men, aged respectively eighteen and twenty-eight years, both showed superficial lymphadenomegaly, and both had responded well to one course of X-ray therapy. In both cases, too, the diagnosis had been confirmed by microscopic examination of sections taken from an enlarged lymph node, after excision and before irradiation.

The first patient, aged twenty-eight years, was suffering from lymphoid follicular reticulosis (Robb-Smith), the so-called follicular lymphoblastoma of American writers. He was seen first at the radiotherapy department in June, 1940, complaining of a lump in the left groin of two and a half years' duration and of another lump in the right side of the neck of three months' duration. On examination he was found to have moderately enlarged lymph nodes in the left groin, extending down as a mass into the femoral region. Smaller nodes were palpable in the left posterior triangle of the neck, in both anterior triangles of the neck and in both axillæ. The spleen was just palpable; there was no great degree of splenomegaly. The Wassermann test produced no reaction. The blood count revealed nothing significant; the erythrocytes numbered 4,650,000 and the leucocytes 7,000 per cubic millimetre. A course of X-ray therapy was administered to six fields (July-August, 1940): to the left and right cervical regions, the left and right axillæ and the left and right groins. The spleen was not irradiated. When seen in October, 1940, the patient showed pronounced clinical improvement, there being definite regression of the enlarged lymph nodes. The patient felt well and had returned to his work. A small node was still just palpable in the left posterior triangle, but altogether the patient's condition was quite satisfactory.

Dr. de Monchaux and Dr. Farrar commented that all patients with lymph nodal enlargement (except when the enlargement was caused by secondary carcinomatous metastasis) responded well, as a rule, to radiotherapy; but as in most cases the prognosis was uncertain and often grave, all such patients had to be kept under close and regular observation.

The second patient suffering from reticulosis was aged eighteen years; he had reported to the department early in July, 1940, with palpable axillary lymph nodes and also enlarged nodes in the left side of the neck and to a less degree in both groins. A blood count revealed no abnormality, and on microscopic examination of one of the enlarged nodes the pathologist reported the condition as histiocytic sinus reticulosis (Robb-Smith) or possibly early Hodgkin's disease. The pathologist stated that it was impossible for him to give a more definite opinion at that early stage. However, the condition was certainly some variety of reticulosis or hyperplasia of lymph nodal tissue. This patient showed no evidence of splenomegaly, which was a clinical feature of differential value in the diagnosis of the reticuloses. X-ray therapy was administered to six fields (August-September, 1940) in the following way: the left and right sides of the neck, the left and right axillæ and the left and right groins. The patient in October, 1940, felt well, had no complaints and had resumed his work. All the enlarged nodes had regressed and none were palpable.

Dr. de Monchaux and Dr. Farrar commented that in this case the question of prognosis was uncertain and the patient had to be observed closely; moreover, further radiotherapy might be necessary in due course.

DR. A. H. TEBBUTT demonstrated the microscopic slides made in these two cases of reticulosis in the pathological department of the hospital.

Hodgkin's Disease.

Finally, Dr. de Monchaux and Dr. Farrar demonstrated the radiographs of a patient suffering from severe Hodgkin's disease, whose condition had been considerably improved in a few weeks by X-ray therapy. The patient was a young girl, aged nineteen years. She had reported recently to the radiotherapy department, complaining of extreme lassitude and a pronounced degree of dyspnœa without cough or sputum. She had been obliged to cease working, and when seen first was very pale and tired looking. Enlarged lymph nodes were present on both sides of the neck, and enlarged abdominal (possibly mesenteric) nodes were noted; on radiographic examination of the chest and mediastinum a large irregular opacity was revealed, extending from the mediastinum into both lung fields and involving both hilar regions also. This opacity undoubtedly represented massive lymph nodal enlargement of the mediastinum and hilar regions of both lungs, the obvious cause of the patient's breathlessness. A radiological diagnosis of Hodgkin's disease was made, which was quite consistent with the clinical findings. The blood count revealed a microcytic anæmia; but unfortunately, up to the time of the meeting, on account of the patient's condition, no enlarged node had been excised for section and microscopic examination. Dr. de Monchaux and Dr. Farrar believed that removal and biopsy of an enlarged lymph node should be carried out in all cases of lymphadenomegaly, except those due to secondary metastasis, when such a node was discrete, accessible and easily removable. For preference the lymph node should be taken from the axilla or from the lower part of the neck (supraclavicular region). After a course of X-ray therapy to the neck and mediastinum (the abdominal nodes were to be irradiated later) this patient showed considerable clinical improvement, with regression of the irradiated nodes. A radiograph of the chest, taken recently for comparison, revealed great improvement in the mediastinal and hilar condition. The regression of the intrathoracic nodes corresponded with a pronounced diminution of the patient's dyspnœa, which had now practically disappeared. She felt much better and stronger, had gained nine pounds in weight since the inception of the course of X-ray treatment, and had resumed her work. Though the condition had not been confirmed microscopically, the features of this case, both clinically and radiographically, strongly suggested a diagnosis of Hodgkin's disease, or *lymphadenoma verum*, which was now regarded as but another variety of reticulosis and classified as such by Robb-Smith in the article referred to earlier.

Herniation of Nucleus Pulposus.

DR. DOUGLAS MILLER showed X-ray photographs and specimens from two recent cases of herniation of a *nucleus pulposus*. The first patient was a female, aged twenty-one years, who a year previously had given her back a severe bump on a "slippery dip". This had been succeeded by constant severe lower back pain and then by sciatica on the right side. Many forms of treatment, including immobilization for three months in a plaster spica, had failed to relieve the pain. On examination she had pronounced bilateral hamstring spasm, and Lasègue's sign was strongly positive on the right side. There was slight relative analgesia over the outer side of the calf. Her reflexes were normal. Stooping was limited and painful. She had a pronounced lumbar curve towards the right. The cerebro-spinal fluid was normal. Plain X-ray films revealed a sacralized fifth lumbar transverse process on the right side. Radiological studies made by means of lipiodol revealed a constant filling defect opposite the fourth intervertebral disk. At operation the fifth lumbar nerve was found to be tightly stretched over a bulging disk, which was removed piecemeal. The patient's recovery was quick, and a fortnight later she was able to walk without pain.

Dr. Miller's second patient was a male, aged fifty years. Six months previously, while driving a motor car, and without sustaining any violence, he had been seized by a severe pain in the left lumbar region. This was completely crippling, and in a few days extended to his left sciatic region. Since then, in spite of much careful treatment in hospital, he had been racked with pain and quite unable to walk. On examination he was found to have bilateral hamstring spasm, and Lasègue's sign was strongly positive on the left side. He stood with a pronounced lumbar curve to the left. There was no alteration in his sensation or reflexes. Plain X-ray films and examination of the cerebro-spinal fluid revealed no abnormality. Radiological studies made by means of lipiodol revealed a constant and obvious filling defect at the fourth lumbar interspace. At operation the fifth nerve was found to be tightly stretched over an intervertebral protrusion, and on incision of the posterior longitudinal ligament a large mass of intervertebral disk could be lifted out free. The patient's relief was immediate, and a fortnight later he was able to stand and walk normally without discomfort.

(To be continued.)

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 36, of February 27, 1941.

AUSTRALIAN MILITARY FORCES.

EASTERN COMMAND.

Second Military District.

Australian Army Medical Corps.

Captain W. Wood from the Reserve of Officers is appointed to the command of 113th General Hospital and to be granted the rank of Lieutenant-Colonel (temporarily), 1st January, 1941.

To be Captains (provisionally).—Matthew Joseph McNamara, 16th January, 1941, and William Patrick Ryan, 20th January, 1941.

SOUTHERN COMMAND.

Third Military District.

Australian Army Medical Corps.

Honorary and Temporary Captain E. T. T. Downie is appointed from the Reserve of Officers (A.A.M.C.), ceases to be seconded with the Department of Defence Co-ordination, relinquishes the temporary rank of Captain, and to be Captain (provisionally), 31st January, 1941.

Honorary Captain E. E. Price is appointed from the Reserve of Officers (A.A.M.C.), and to be Captain (provisionally), with regimental seniority next after Captain H. D. B. Miller, 1st July 1940 (in lieu of the notification respecting this officer which appeared in Executive Minute No. 169/1940, promulgated in *Commonwealth Gazette*, No. 181, of 1940).

Captain G. H. Dallimore is transferred to the Reserve of Officers (A.A.M.C.), 22nd January, 1941.

To be Captains (provisionally).—John Kelvin Gardner and Roderick Frank Arthur Strang, 31st January, 1941.

Australian Army Medical Corps Reserve.

To be Honorary Captains.—Muir Jack Myer Lapin, 29th January, 1941, and Arthur William Burton, 31st January, 1941.

Fourth Military District.

Australian Army Medical Corps.

Honorary Captains A. J. Blofeld-Moody and C. H. Schafer are appointed from the Reserve of Officers (A.A.M.C.), and to be Captains (provisionally), 17th July, 1940, and 26th July, 1940, respectively (in lieu of the notifications respecting these officers which appeared in Executive Minute No. 169/1940, promulgated in *Commonwealth Gazette* No. 181 of 1940).

Australian Army Medical Corps Reserve.

To be Honorary Captains.—Robert Myer Hains, 27th December, 1940, and William Andrew Dibden, 23rd January, 1941.

Sixth Military District.

Australian Army Medical Corps Reserve.

To be Honorary Captains.—James Thomas Brook, 31st October, 1940 (in lieu of the notification respecting this officer which appeared in Executive Minute No. 235/40, promulgated in *Commonwealth Gazette* No. 1 of 1941), John Frederick McCreary, 30th November, 1940, Alexander John Middleton White, 11th January, 1941, and Louis Lancelote Oxley Bevan, 16th January, 1941.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force.

Medical Branch.

Kenneth Eden Shellshear, M.R.C.S. (Eng.), L.R.C.P. (Lon.), is granted a commission on probation with the temporary rank of Squadron Leader, with effect from 27th January, 1941.

Obituary.

ERIC BAILHACHE.

WE are indebted to Dr. H. Boyd Graham for the following appreciation of the late Major Eric Bailhache.

By the death of Dr. Eric Bailhache, which occurred on February 26, 1941, the members of the Victorian Branch of the British Medical Association have sustained the first loss on active service abroad. Dr. Bailhache was reported to have been wounded and to have died from septicæmia.

He was a son of the late Herbert Bailhache, of the State Savings Bank, and married the youngest daughter of the late Henry Andrews, of Melbourne. He was forty-two years of age at the time of his death, and is survived by a widow and three young daughters, to whom we extend our heartfelt sympathy.

Eric Bailhache was educated at Scotch College and enlisted in the Great War a few days after leaving school. On his return he entered upon the medical course at the University of Melbourne and graduated in 1924. After serving as resident medical officer at the Royal Melbourne Hospital, he went into practice at Alexandra for a short time and later practised at Brighton for some years. Recently he spent two years in London and Vienna on post-graduate work in gynæcology and obstetrics. Before enlisting for active service he had commenced the practice of his specialty and was a clinical assistant both at Prince Henry's Hospital and at the Women's Hospital.

While at the University, Eric Bailhache was a member of the Melbourne University Rifles and represented Ormond College at tennis and hockey. Previous to the outbreak of the present war he had a record of some years' service in the militia, and within a few days of the declaration of war he enlisted and entered camp. While undergoing training he was promoted to the rank of major and left for a theatre of war in April of last year as an officer in a field ambulance.

Having seen active service in the last war and given his life in this one, he has left a record which will be an inspiration to us all.

KEITH RUSSELL MOORE.

WE regret to announce the death of Dr. Keith Russell Moore, which occurred on March 1, 1941, at Perth, Western Australia.

GEORGE GORDON OWEN PHILLIPS.

WE regret to announce the death of Dr. George Gordon Owen Phillips, which occurred on March 7, 1941, at Sydney, New South Wales.

Correspondence.

A METHOD OF COVERING SKIN GRAFTS.

SIR: Choyce's system of surgery suggests as a covering for skin grafts (i) a layer of protective or (ii) perforated silver foil which is placed over the grafts before the dressing is applied. Other coverings applied next to the grafts, which Choyce recommends, are "Leno" (an open-wove calico impregnated with starch) or sterilized muslin such as is used to make mosquito curtains.

The use of green oiled silk as a protective, with rows of perforations cut laboriously with scissors, has given fairly satisfactory "takes" of grafts and combines the good points of the first two suggestions made by Choyce—namely, a covering with perforations in it. Much time can be saved, however, and rows of evenly spaced circular holes can be made in the oiled silk by folding the piece into a long narrow pad about three-quarters of an inch wide and then punching, say, two parallel rows through the whole thickness of the oiled silk, the punch marks being about one-eighth of an inch from each other, and removing small circular pieces of the oiled silk corresponding in number to the number of times the oiled silk has been folded.

The punch used is the type which is used by saddlers for punching leather (called a spring leather punch). The oiled silk thus perforated seems to settle down firmly on the grafts, holding them securely, especially if the corners and edges are partly strapped down with one-inch "Elastoplast". Exudation from the grafted area also has free escape through the perforations into saline-soaked pads of gauze covered with lint and wool, which are held with light pressure against the grafted area by three-inch "Elastoplast" bands taped and tied across the centre of the dressing.

The after-care consists of keeping the saline pad soaked frequently with warm saline poured from an undine, and every twenty-four hours the gauze and lint pad is changed.

In four or five days the oiled silk is removed and replaced by a fresh one sterilized by boiling, and the saline pads are changed two or three times in each twenty-four hours, the oiled silk thereafter being changed each day, and this is kept up until the grafted area is completely epithelialized.

Local anæsthesia has proved effective in anæsthetizing the skin from which the grafts are taken, an oblong-shaped area being fenced off by intradermal injections of "Adrocaine" along the boundaries, and this is supplemented by ten cubic centimetres or so of 0·5% "Novocain" injected at numerous points underneath this area of skin from which the grafts are to be shaved.

Yours, etc.,

C. D. BATEMAN, M.B., Ch.M.

16, Kable Street,
Windsor,
New South Wales.

March 3, 1941.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Perkman, Salme, M.B., B.S., 1939 (Univ. Sydney), St. George District Hospital, Kogarah.

The undermentioned has applied for election as a member of the Tasmanian Branch of the British Medical Association:

Gollan, Lachlan Neil, M.B., B.S., 1936 (Univ. Melbourne), 11, Norfolk Crescent, Sandy Bay.

Corrigendum.

WE are informed by Dr. T. E. Wilson that an error has occurred in his paper entitled "Bone Marrow Changes in Acute Infections and the Effects of Sulphonamides on the Marrow", which appeared in the issue of March 1, 1941. The mistake is at page 263, in the first column and the fifth line from the bottom of the page; the sentence beginning "The fatal issue did appear to be hastened . . ." should read "The fatal issue did not appear to be hastened . . ." We apologize to Dr. Wilson for this error.

Diary for the Month.

MAR. 17.—Victorian Branch, B.M.A.: Hospital Subcommittee.
MAR. 18.—Queensland Branch, B.M.A.: Ear, Nose and Throat Section.
MAR. 18.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAR. 18.—Victorian Branch, B.M.A.: Organization Subcommittee.
MAR. 18.—Victorian Branch, B.M.A.: Finance, House and Library Subcommittee.
MAR. 19.—Western Australian Branch, B.M.A.: Branch.
MAR. 20.—Queensland Branch, B.M.A.: Ipswich Hospital Clinical Society.
MAR. 20.—Victorian Branch, B.M.A.: Executive.
MAR. 25.—New South Wales Branch, B.M.A.: Council, Quarterly.
MAR. 26.—Victorian Branch, B.M.A.: Council.
MAR. 27.—New South Wales Branch, B.M.A.: Annual.
MAR. 27.—South Australian Branch, B.M.A.: Branch.
MAR. 28.—Queensland Branch, B.M.A.: Council.
MAR. 28.—Tasmanian Branch, B.M.A.: Council.
APR. 1.—Queensland Branch, B.M.A.: Post-Graduate Committee.
APR. 1.—New South Wales Branch, B.M.A.: Council.
APR. 2.—Western Australian Branch, B.M.A.: Council.
APR. 2.—Victorian Branch, B.M.A.: Branch.
APR. 3.—South Australian Branch, B.M.A.: Council.
APR. 4.—Queensland Branch, B.M.A.: Branch.
APR. 4.—Victorian Branch, B.M.A.: Legislation Subcommittee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia: all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such a notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rates are £2 for Australia and £2 5s. abroad *per annum* payable in advance.